The American Journal of Cardiology®

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COK-H01241-86-P024212

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Destination: CHD

Triad patients are at increased risk of heart attack[1,2]

In the placebo population of the Helsinki Heart Study, patients with the triad of risk—low HDL, elevated LDL, and elevated triglycerides—have been shown to be almost four times more likely to develop CHD.[1]

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CHDetour:

LOPID reduced CHD* by 57% in triad patients[†]

In the Helsinki Heart Study, LOPID reduced heart attack by 57% in patients at very high risk and by 34% overall.[‡] LOPID raises HDL and lowers LDL and triglycerides while it reduces the risk of developing CHD as an adjunct to diet in patients with the triad of lipid abnormalities who have had an inadequate response to exercise, dietary therapy, weight loss, and trial of other pharmacologic agents (such as bile acid sequestrants and nicotinic acid).

LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in type IIb patients who are without history of or symptoms of existing coronary heart disease **and** who have the following triad of lipid abnormalities: low HDL cholesterol in addition to elevated LDL cholesterol and elevated triglycerides.

In addition, the potential benefit of gemfibrozil in treating type IIa patients with elevations of LDL cholesterol only is not likely to outweigh the risks. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

57%

With baseline HDL above the median (46.4 mg/dL), the incidence of serious coronary events was similar for LOPID and placebo groups.

*Defined as a combination of definite coronary death and/or definite myocardial infarction. 57% calculated from an incidence of CHD of 149/1000 among placebo patients and 64/1000 among treated patients.

[†] Baseline LDL >175 mg/dL, baseline TG >200 mg/dL, and baseline HDL <35 mg/dL.

[‡] All patients were counseled on dietary therapy and encouraged to exercise and quit smoking.

Please see adjacent page for brief summary of prescribing information.

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CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. See CLINICAL PHARMACOLOGY section in full prescribing information which includes the following: The secondary prevention component of the Helskinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, $p=0.14$). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the Lopid group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, $p=0.06$). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients *without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either

species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis	1.2	0.6
(histologically confirmed in most cases where data were available)		
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20	Bottles of 60
N 0071-0737-30	Bottles of 500
N 0071-0737-40	Unit dose packages of 100 (10 strips of 10 tablets each)

Parcode® No. 737

Storage: Store below 30° C (86° F).

REFERENCES

1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245.
2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651.
3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury JB et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.
4. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988;148:36-39.

Caution – Federal law prohibits dispensing without prescription. 0737G015

Revised April 1992

REFERENCES:

1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.
2. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). *Am J Cardiol.* 1992;70:733-737.

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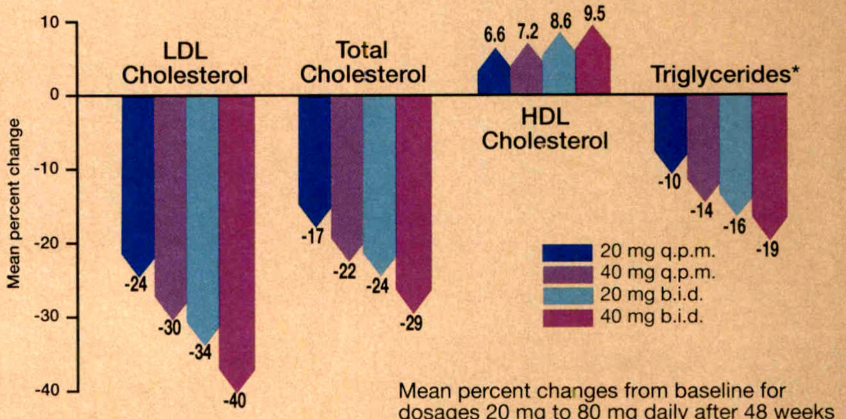

Mean percent changes from baseline for dosages 20 mg to 80 mg daily after 48 weeks of treatment (n=6,582)

* Triglyceride values are expressed as median changes.

1. Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, Arch. Intern. Med. *151*:43-49, January 1991.

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MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR®*
(LOVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m^2

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported, no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.

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J1MC56(519)

The American Journal of Cardiology®

JANUARY 1, 1993, VOL. 71, NO. 1

CORONARY ARTERY DISEASE

1

Patency of the Infarct-Related Artery and Left Ventricular Function as the Major Determinants of Survival After Q-Wave Acute Myocardial Infarction

Marcello Galvani, Filippo Ottani, Donatella Ferrini, Francesco Sorbello, and Franco Rusticali

One hundred seventy-two patients recovering from Q-wave acute myocardial infarction were followed for up to 10 years to assess the prognostic significance of the patent infarct-related artery. All patients were studied by coronary angiography before hospital discharge and selected on the basis of the presence of 1-vessel disease. Among several clinical and angiographic variables, multivariate logistic regression analysis identified patency of the infarct-related artery and end-systolic volume index as independent predictors of survival. Patency of the infarct-related artery was also the only independent determinant of nonfatal recurrent ischemia. During follow-up, no deaths were observed among patients without left ventricular (LV) dysfunction, irrespective of vessel patency. In the subset with LV dysfunction, mortality was 30% among patients without anterograde perfusion compared with 2% among those with preserved flow. This finding suggests the need for specific treatment strategies in patients with an occluded infarct-related artery and damaged LV function.

8

Comparison in Acute Myocardial Infarction of Anisoylated Plasminogen Streptokinase Activator Complex Versus Heparin Evaluated by Simultaneous Thallium-201/Technetium-99m Pyrophosphate Tomography

Thomas Krause, Wolfgang Kasper, Thomas Meinertz, Markus Schnitzler, Hanjörg Just, Carl Schümichen, and Ernst Moser

In a subgroup of 45 patients with acute myocardial infarction from the German multicenter trial of anisoylated plasminogen streptokinase activator complex (APSAC) (n = 20) versus heparin (n = 25), simultaneous thallium (Tl)-201 technetium (Tc)-99m pyrophosphate (PYP) tomography was initiated to elucidate a possible benefit of APSAC over heparin. Findings in the 2 treatment groups were similar with respect to coronary patency, Tl-201 defect score, relative scintigraphic infarct size, global ejection fraction, maximal creatine kinase level, and 2 different Tl-201/Tc-99m PYP accumula-

tion patterns (homogeneous and inhomogeneous). However, patients with an inhomogeneous Tl-201/Tc-99m PYP accumulation pattern had a higher incidence of in-hospital complications than patients with a homogeneous pattern. Scintigraphic infarct size and Tl-201 defect score were greater in patients with the above-mentioned clinical events. In addition to scintigraphic infarct size and coronary patency, the Tl-201/Tc-99m PYP accumulation pattern was useful in differentiating patients with from those without an adverse clinical course.

14

Blood Viscosity During Thrombolytic Therapy with Anistreplase in Acute Myocardial Infarction

Johannes J. M. L. Hoffmann, Johannes J. R. M. Bonnier, Paul G. Melman, and Ingrid Bartholomeus

This study documents the changes in viscosity of blood and plasma, in hematocrit and in plasma fibrinogen during thrombolytic therapy with anistreplase in 10 patients with acute myocardial infarction. In addition, coronary angiography was performed in order to assess cardiac output after 90 minutes and 48 hours. Within 30 minutes from starting thrombolytic therapy, significant reductions in viscosity, hematocrit and fibrinogen were recorded, which lasted for about 2 days. Subsequently, blood and plasma viscosity markedly increased, mainly as a result of fibrinogen rebound. In multiple regression analysis, the hematocrit appeared to be the most important determinant of blood viscosity, followed by fibrinogen. Cardiac output was not correlated with the striking changes in blood rheology.

19

Effects of Late (1 to 30 Days) Reperfusion After Acute Myocardial Infarction on the Signal-Averaged Electrocardiogram

Michael Ragosta, Peter J. Sabia, Sanjiv Kaul, John P. DiMarco, Ian J. Sarembock, and Eric R. Powers

To study the effect of late reperfusion (>24 hours) after acute myocardial infarction on the signal-averaged electrocardiogram (SAECG), SAECGs, echocardiograms and thallium-201 images on 41 patients were obtained before and 1 month after angioplasty of the occluded infarct-related artery. Angioplasty, performed 12 ± 8 days after infarction, was successful in 32 patients and unsuccessful in 9. There was no change in the incidence of late potentials after successful reperfusion (13 of 32 patients before and 13 of 32 patients 1 month later) or after unsuccessful reperfusion (6 of 9 patients before and 5 of 9 patients 1 month later). No effect was seen on the QRS duration or the terminal signal duration $<40\ \mu V$ in patients with successful reperfusion; a small improvement in the terminal root-mean-square voltage was observed. Among patients with successful reperfusion, those without late potentials at baseline had improved wall motion to a greater extent than those with late potentials, suggesting that the presence of viable myocardium is associated with less abnormalities on the SAECG. It is concluded that the SAECG does not change after late reperfusion and that a normal SAECG is associated with viable myocardium.

24

Ventricular Arrhythmias in Rehabilitated and Nonrehabilitated Post–Myocardial Infarction Patients with Left Ventricular Dysfunction

Harry L. Hertzeanu, Joseph Shemesh, Leon A. Aron, Anabela L. Aron, Edna Peleg, Talma Rosenthal, Michael Motro, and Jan J. Kellermann

The incidence of ventricular arrhythmias in rehabilitated post–myocardial infarction patients with left ventricular dysfunction (ejection fraction <40%) in a long-term rehabilitation program (arm training and calisthenics) was assessed and compared with that in similar patients who were not in any rehabilitation program. There were no statistically significant differences concerning age, ejection fraction, location of myocardial infarction, and antiarrhythmic therapy. After 36 and 60 months, an improvement in hemodynamic condition of patients in the arm training group was observed. Quality of life was higher in the rehabilitated patients, with a high percentage of return to work (82 vs 40%). The lowest levels of norepinephrine were found in the arm training group and the highest in the nonrehabilitated group ($p < 0.02$), whereas they were within normal limits in the calisthenic group. More isolated ventricular premature beats ($p < 0.05$), complex ventricular arrhythmias ($p < 0.05$) and episodes of nonsustained ventricular tachycardia ($p < 0.03$) were found in nonrehabilitated patients than in rehabilitated ones. It appears that a long-term rehabilitation program decreases neuroadrenergic activity, the arrhythmogenic effect of catecholamines and consequently, the incidence of ventricular arrhythmias.

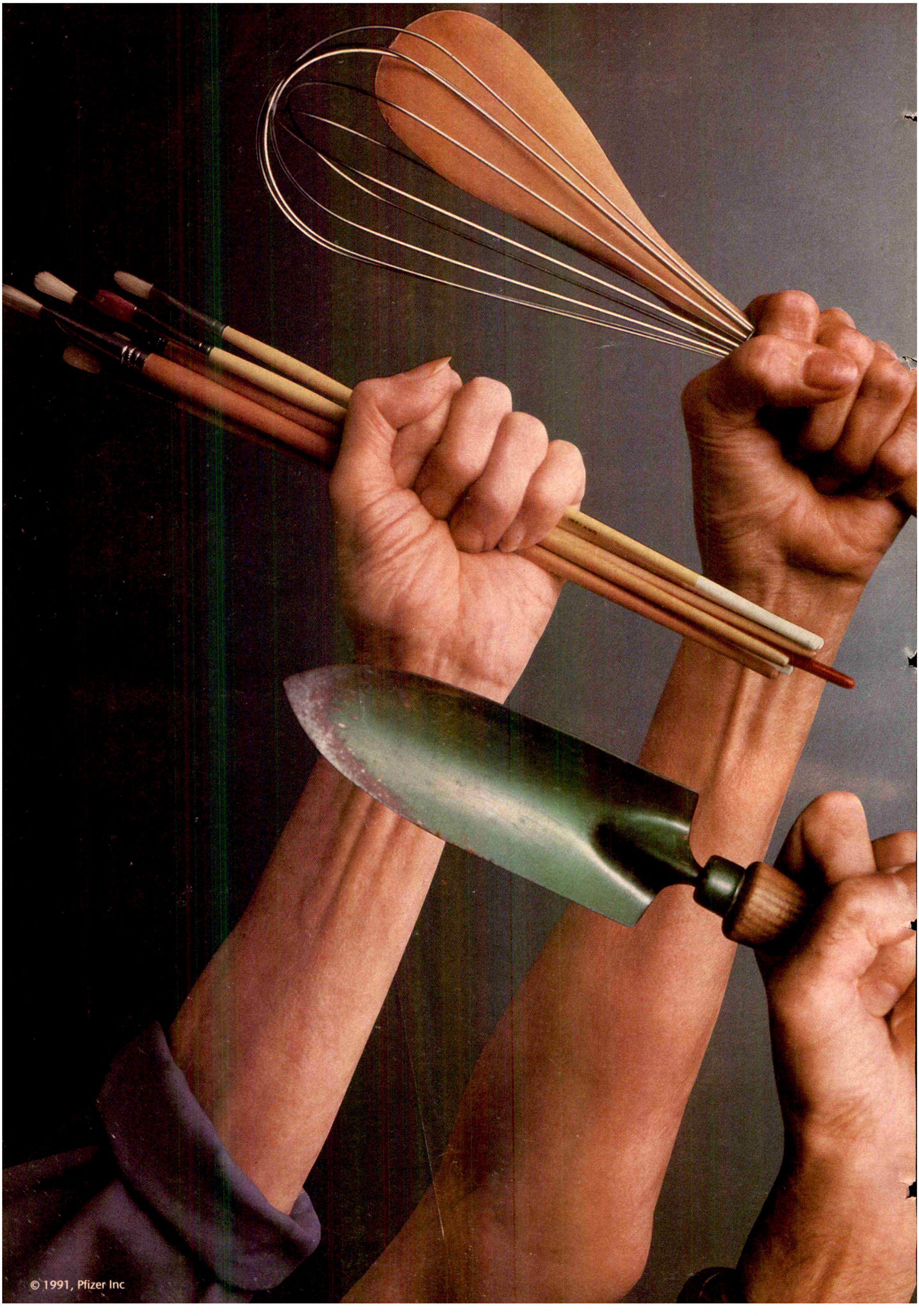
28

Validation by High-Frequency Epicardial Echocardiography of a New Method of Analyzing Coronary Angiography Quantitatively in Coronary Artery Disease

David D. McPherson, Maryl R. Johnson, Steven M. Collins, Robert A. Kieso, Melvin L. Marcus, and Richard E. Kerber

The purpose of this project was to compare coronary arterial lumen areas measured by quantitative coronary angiography with measurements obtained by high-frequency epicardial echocardiography. Quantitative coronary angiography correlated well with high-frequency echo measurements of lumen area. Traditional angiographic percent stenosis measurements did not agree well with high-frequency epicardial echocardiography. These data question the validity of traditional angiographic percent diameter lumen stenosis measurements as an accurate estimation of coronary atherosclerotic obstruction but confirm that quantitative coronary angiographic estimates accurately predict residual lumen area.

Continued on page A15



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Procardia XL®
(nifedipine) Extended Release
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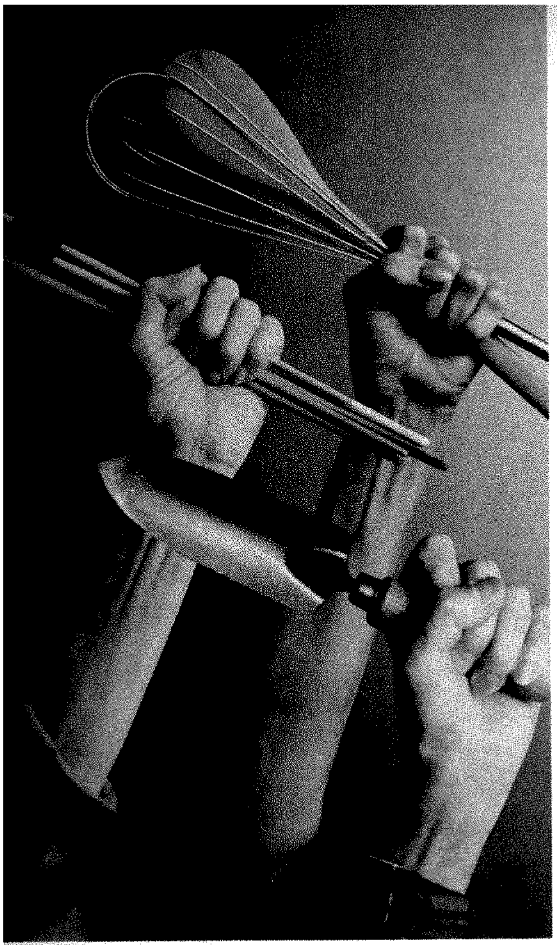

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- Start patients on a single 30-mg or 60-mg PROCARDIA XL Extended Release Tablet, swallowed whole, once a day
- In patients with angina, doses above 90 mg should be used with caution and only when clinically warranted
- Side effects include peripheral edema, which is not associated with fluid retention, and headache

PROCARDIA XL Also Provides Confident 24-Hour Control of Elevated Blood Pressure[3]

- In patients with hypertension, doses above 120 mg are not recommended

References:
1. Chung M, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: a controlled-release formulation of nifedipine. *Am J Med.* 1987;83(suppl 6B):10-14. **2.** Bittar N. Usefulness of nifedipine for myocardial ischemia and the nifedipine gastrointestinal therapeutic system. *Am J Cardiol.* 1989;64:31F-34F. **3.** Bravo EL, Krakoff LR, Tuck MK, Friedman CP, the MATH Study Group. Effects of nifedipine gastrointestinal therapeutic system (NGITS) in older (O) and younger (Y) essential hypertensives. *Clin Pharmacol Ther.* 1990;47:199. Abstract.

Brief Summary
PROCARDIA XL®(nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request. Revised July 1990

Pfizer Labs

33

Prognostic Value of Dobutamine Echocardiography in Patients with High Pretest Likelihood of Coronary Artery Disease

Peter K. Mazeika, Aleksander Nadazdin, and Celia M. Oakley

To examine the value of transient regional asynergy on dobutamine echocardiography as a noninvasive predictor of future cardiac events, 51 symptomatic patients with high pretest probability of coronary artery disease were studied using infusion rates up to 20 μg/kg/min. During 24 ± 4 months of follow-up, 23 patients had events (1 myocardial infarction, 9 unstable angina, 10 coronary bypass grafting, 3 coronary angioplasty). Transient asynergy was seen in 17 of 23 patients (74%) with and 8 of 28 patients (29%) without events ($p < 0.01$); 5 of 6 patients (83%) with involvement of 3 left ventricular segments had events. Myocardial infarction or unstable angina occurred in 8 of 25 patients (32%) with a positive and 2 of 26 patients (8%) with a negative stress echocardiogram ($p < 0.05$). Patients with probable coronary artery disease and a positive dobutamine echocardiogram appear at higher risk of an adverse outcome. This test may aid selection for coronary angiography and prognostic revascularization, particularly in patients unable to exercise.

40

Prognostic Value of Noninvasive Cardiac Tests in the Assessment of Patients with Peripheral Vascular Disease

Edward L. Rose, Xiu J. Liu, Michael Henley, John D. Lewis, Edward B. Raftery, and Avijit Lahiri, with the technical assistance of Usha Raval

Two hundred thirty-six patients with peripheral vascular disease were prospectively studied to assess whether noninvasive cardiac investigations could predict prognosis better than simple clinical assessment. Clinical history, examination and resting electrocardiography, exercise electrocardiography, Holter monitoring, radionuclide ventriculography and dipyridamole thallium imaging were performed. Follow-up for 6 to 30 months revealed major cardiac events in 21 patients. Cox survival analysis demonstrated that clinical coronary artery disease was the best variable that predicted cardiac events with no help from other clinical variables. When noninvasive cardiac assessment was added, dipyridamole thallium heart:lung ratio and left ventricular ejection fraction added incrementally to the prediction of cardiac events. Results of exercise electrocardiography or Holter monitoring did not help. It is concluded that high lung uptake of thallium during dipyridamole stress and impaired left ventricular ejection fraction assist in identifying patients with peripheral vascular disease who are at higher cardiac risk and should therefore be used in deciding subsequent management.

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Rationale and Design of the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (HIT) for Secondary Prevention of Coronary Artery Disease in Men with Low High-Density Lipoprotein Cholesterol and Desirable Low-Density Lipoprotein Cholesterol

Hanna Bloomfield Rubins, Sander J. Robins, Marika K. Iwane, William E. Boden, Marshall B. Elam, Carol L. Fye, David J. Gordon, Ernst J. Schaefer, Gordon Schectman, and Janet T. Wittes, for the Department of Veterans Affairs HIT Study Group

This study describes the rationale and design of the Department of Veterans Affairs High-density Lipoprotein (HDL) Intervention Trial (HIT), a multicenter, randomized, controlled clinical trial designed to determine whether lipid therapy reduces the combined incidence of coronary artery disease (CAD) death and nonfatal myocardial infarction in men with established CAD who have low levels of HDL cholesterol with "desirable" levels of low-density lipoprotein cholesterol. Twenty-five hundred men with CAD and this lipid profile are being recruited at 20 Department of Veterans Affairs medical centers, randomized to either gemfibrozil or placebo, and followed in a double-blind manner for an average of 6 years. Since an estimated 20 to 30% of men with CAD have low HDL cholesterol as their primary lipid abnormality, the results of this trial are expected to have far-reaching clinical implications.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Comparison of Effects of Propranolol Versus Pindolol on Sinus Rate and Pacing Frequency in Sick Sinus Syndrome

S. Adam Strickberger, R. David Fish, Gervasio A. Lamas, Catherine Cantillon, Satinder Bhatia, Noreen McGowan, Elliott M. Antman, and Peter L. Friedman

Beta blockers in patients with sick sinus syndrome (SSS) may prevent supraventricular arrhythmias, systemic hypertension and ischemia, but may cause excessive depression of sinus node function. Beta blockers with intrinsic sympathomimetic activity may be advantageous. In a double-blind crossover trial in 8 patients with SSS and a permanent pacemaker, the effect of pindolol on bradycardia was compared with that of propranolol. Holter monitors were used to evaluate the frequency of pacing and ambulatory sinus heart rates. When treated with pindolol rather than propranolol, the maximal ambulatory sinus heart rate was 30% higher ($p = 0.02$), while the amount of pacing per day was reduced by 54% ($p = 0.04$). Therefore, treating SSS patients with β blockers with intrinsic sympathomimetic activity may result in less bradycardia than treatment with conventional β blockers. In some patients this may help to prevent prophylactic pacemaker implantation, and for patients already with VVI pacemakers, chronotropic incompetence and pacemaker syndrome as well.

Continued on page A19

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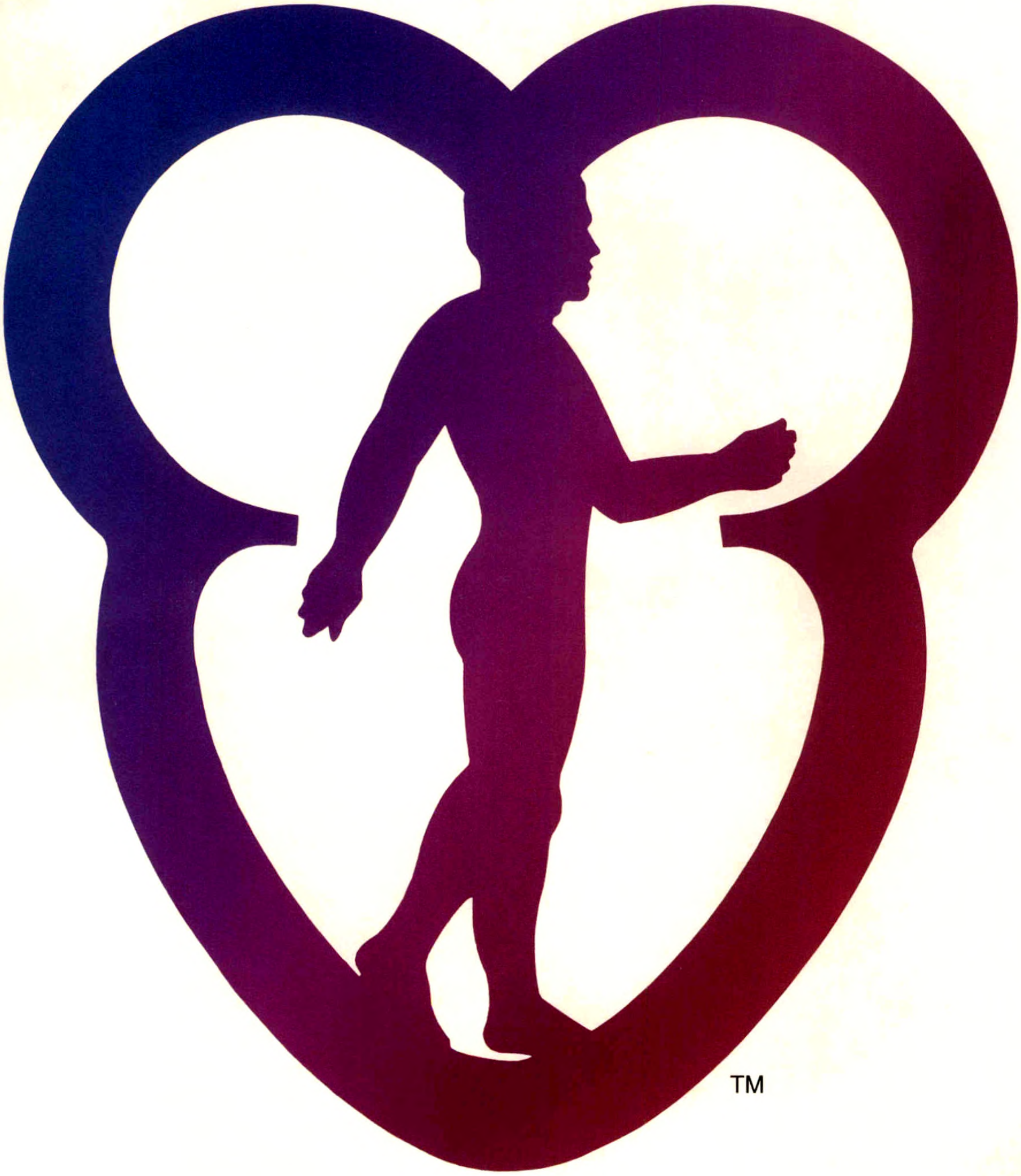

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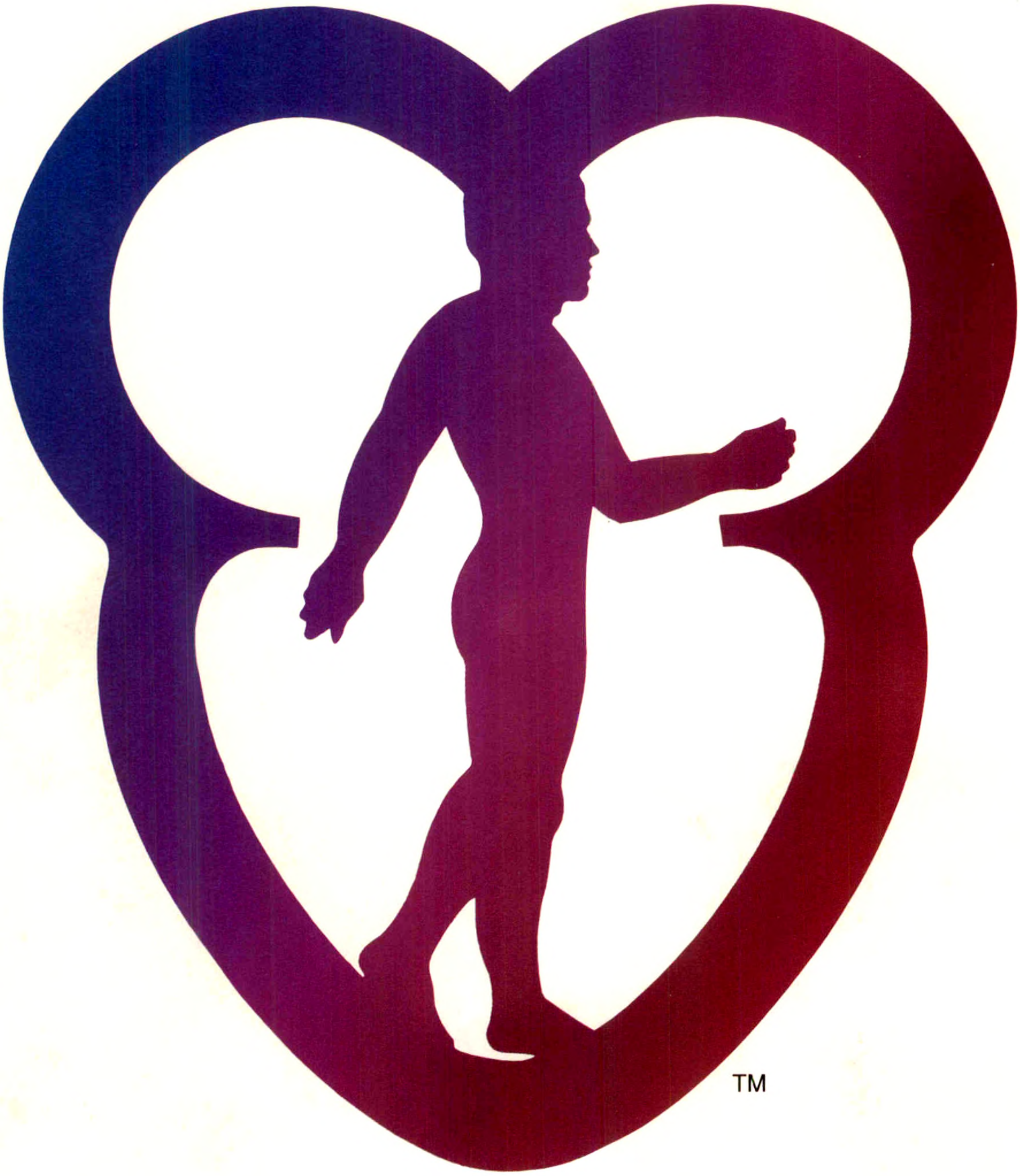

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Morphologic Characteristics of Nonsustained Ventricular Tachycardia Detected During Holter Monitoring Associated with Atherosclerotic Coronary Artery Disease

Pablo Denes

The morphologic features of nonsustained ventricular tachycardia (VT) were examined by obtaining a derived 12-lead electrocardiogram (ECG_D) from a 24-hour Holter recording in 22 patients with nonsustained VT and coronary artery disease. A total of 60 nonsustained VT episodes were recorded. Of these, 20 were uniform and 40 were multiform. Mean rate of uniform episodes was faster (140 ± 32 vs 124 ± 16 beats/min; $p < 0.01$) and the duration longer (5.3 ± 2.0 vs 4.0 ± 1.0 beats; $p < 0.02$) than the multiform episodes. Six (30%) of the uniform episodes had an irregular rate resembling atrial fibrillation. The majority (87%) of multiform episodes had only 2 different QRS morphologies on the ECG_D. Four unique patterns of QRS morphologies were found within individual multiform nonsustained VT runs. Patients with multiple episodes of nonsustained VT frequently had differing patterns and morphologies between episodes. Further studies are needed to evaluate the clinical usefulness of the information in the management of patients with nonsustained VT.

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Delayed Restoration of Atrial Function After Conversion of Atrial Flutter by Pacing or Electrical Cardioversion

Luc Jordaens, Luc Missault, Eric Germonpré, Benedict Callens, Luc Adang, Johan Vandenbogaerde, and Denis L. Clement

A prospective study was performed with echo-Doppler to evaluate diastolic transmitral flow in 22 patients with atrial flutter before and after conversion to sinus rhythm. Conversion was performed in a randomized way with either overdrive pacing or 50 J shocks. A backup shock of 200 J was delivered if the former methods were unsuccessful. Atrial filling fraction and peak velocity of late diastolic filling were reduced immediately after conversion (with each method). Both parameters gradually increased over time within 24 hours. Further significant improvement of atrial function was observed after 6 weeks. No differences between overdrive pacing and electrical cardioversion were detected.

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Use of Multiple Patches During Implantation of Epicardial Defibrillator Systems

Jeffrey M. Baerman, Bradford P. Blakeman, Brian Olshansky, Douglas E. Kopp, John G. Kall, and David J. Wilber

Of 236 consecutive epicardial defibrillator implantations at our institution, 18 patients had implantation of either a 3- (n = 15) or 4- (n = 3) defibrillator patch system. In the 18 patients who eventually had placement of a multiple-patch system, the best 2-patch defibrillation energy requirement was >18 J in 4 patients, >20 J in 2 patients, ≥30 J in 9 patients, and >40 J in 3 patients. With the multiple-patch system, the defibrillation energy requirement was ≤24 J in 1 patient, ≤20 J in 5 patients, ≤18 J in 8 patients, ≤15

J in 2 patients, and ≤10 J in 2 patients. This improvement was significant (p <0.005). With 11.4 ± 5.6 months of follow-up, no adverse consequences occurred from use of these multiple-patch systems.

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Impaired Immediate Vasoconstrictor Responses in Patients with Recurrent Neurally Mediated Syncope

James F. Sneddon, Peter J. Counihan, Yaver Bashir, Guy A. Haywood, David E. Ward, and A. John Camm

Immediate responses to head-up tilt were determined in 78 consecutive patients with unexplained syncope undergoing 45-minute tilt tests at 60°. Thirty-four patients developed neurally mediated syncope (mean time to syncope 18 minutes), and 40 tolerated the full duration of tilt. Blood pressure, heart rate, and forearm blood flow and vascular resistance were measured at baseline and after 2 and 5 minutes of tilt. There was no difference between the groups in heart rate or blood pressure at 2 minutes, but at 5 minutes, there was a small but significant percent reduction in mean arterial pressure from baseline in syncopal patients. In syncopal patients, forearm vascular resistance was 51.0 and 44.0 at 2 and 5 minutes, respectively, whereas in nonsyncopal patients, it was 82.4 (p <0.02) and 73.1 (p <0.001), respectively. Patients with tilt-induced syncope have clearly demonstrable abnormalities in vascular control immediately after assumption of the upright posture. The results shed new light on the pathophysiology of neurally mediated syncope.

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A Population-Based Estimate of Candidacy Rates for the Implantable Cardioverter-Defibrillator

Thomas E. Kottke, Marshall S. Stanton, Kent R. Bailey, Wyatt W. Decker, and Stephen C. Hammill

A retrospective review of medical records was performed in a defined population to estimate the candidacy rates for implantable cardioverter-defibrillators (ICDs). Subjects were defined as noncandidates, possible candidates and definite candidates on the basis of American Heart Association/American College of Cardiology guidelines. Candidacy rates for this population ranged from 3.3/100,000 (counting only definite candidates from 1976 to 1988) to 8.7/100,000 (counting definite and possible candidates from 1980 to 1988). It was found that half of all deaths among candidates had the potential to be delayed by an ICD. In a similar population with death rates from heart disease of approximately 280/100,000, 0.6 to 1.6% of subjects have the potential to have their deaths delayed to some extent by an ICD. Extrapolated to the 1990 United States population, it is estimated that 8,207 to 21,637 subjects become device candidates each year.

Continued on page A23

In life-threatening recurrent VT or VF refractory to conventional antiarrhythmic agents

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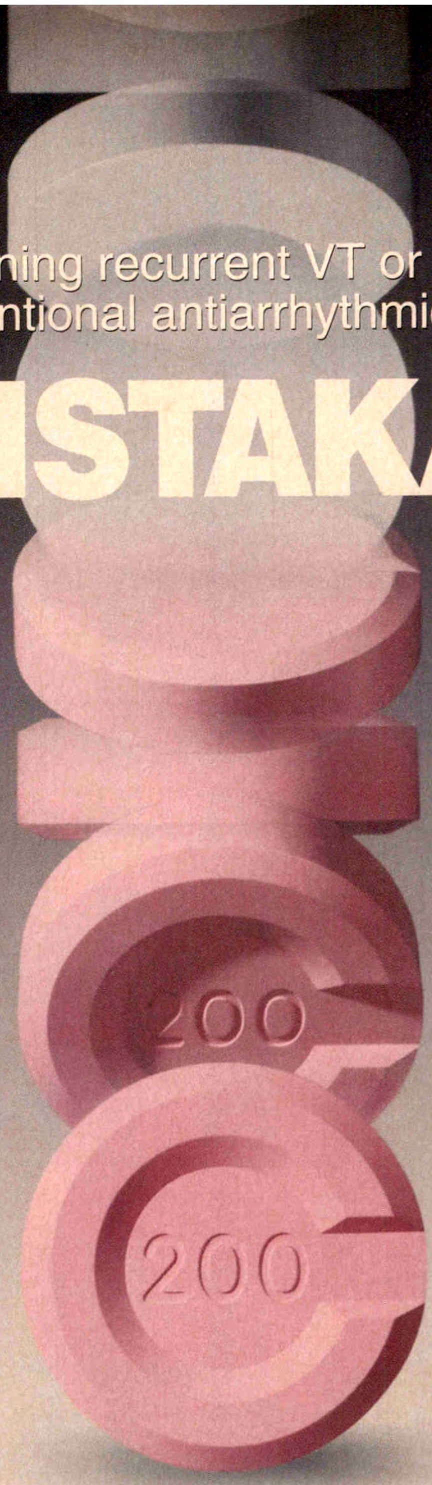

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Cordarone® is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by serious adverse reactions.

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See adjacent page for brief summary of prescribing information.

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Cordarone® (amiodarone HCl) Tablets

BRIEF SUMMARY

(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Controlled trials show no evidence that Cordarone favorably affects survival.

For use only by physicians familiar with and with access to (directly or via referral) all available modalities for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential arrhythmia exacerbation, start Cordarone in a hospital setting.

Contraindications: Severe sinus-node dysfunction, with marked sinus bradycardia; 2nd- and 3rd-degree atrioventricular (AV) block; episodes of bradycardia which cause syncope (except when used with a pacemaker); known hypersensitivity to the drug.

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/ alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium-scan and pathological data consistent with pulmonary toxicity; frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Preexisting pulmonary disease does not appear to increase risk of toxicity; however, prognosis is poorer if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from indirect (hypersensitivity pneumonitis) or direct (interstitial/alveolar pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when a T suppressor/cytotoxic (CD8 - positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis, characterized by diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsies. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity; however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the first week; most clinical improvement was in first 2-3 weeks. Chest X-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-60 mg/day) or equivalent doses of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a possibility of pulmonary toxicity; repeat and evaluate history, PE, chest X-ray, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as decreases in diffusion capacity approach 30%, sensitivity decreases but specificity increases. A diagnostic gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, start steroids and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series), includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients

LIVER INJURY: Increased hepatic enzymes, mostly asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline Rarely, hepatic failure has been fatal

PREGNANCY — PREGNANCY CATEGORY D Cordarone is embryotoxic (increased fetal resorption and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose Similar results are seen in one mice strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor rabbits at doses up to 9 times the maximum recommended maintenance dose

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. There are some reports of congenital goiter/ hypothyroidism and hyperthyroidism. If used anytime during pregnancy apprise patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discernible only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped; if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients; sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin Fair complexion or excess sun exposure may increase risk; also may be related to cumulative dose and therapy duration.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-10% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy; may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia breakthrough or aggravation. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers and/or temporary steroid therapy may be needed. (See full prescribing information for additional information regarding treatment).

SURGERY: ***Hypotension Postbypass:*** Rarely, hypotension is seen on cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy; rarely, the outcome is fatal. The mechanism may be generation of superoxide radicals during oxygenation; therefore, keep operative FiO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGOT and SGPT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hepatomegaly occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, a potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin

Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%, onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55% (n-acetyl procainamide by 33%) in < 7 days. In general, reserve such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone, when arrhythmia suppression should be starting. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats. Incidence greater than control even at lowest dose tested, i.e., about 1/2 the highest recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breast-feeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 400 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; rates appear relatively constant beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cardiac conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 10-33% of patients: GI–Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic–Solar dermatitis/photosensitivity; Neurologic–Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI–Constipation, anorexia; Ophthalmologic–Visual disturbances; Hepatic–Abnormal liver-function tests; Respiratory–Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid–Hypo- or hyperthyroidism; Neurologic–Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular–CHF, cardiac arrhythmias, SA node dysfunction; GI–Abdominal pain; Hepatic–Nonspecific hepatic disorders; Other–Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include visual disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>3,000 mg/kg).

Along with general supportive measures, monitor patient's cardiac rhythm and blood pressure; if bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

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4008-2 Revised October 18, 1990

SYSTEMIC HYPERTENSION

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Efficacy and Tolerability of Lovastatin in Hypercholesterolemia in Patients with Systemic Hypertension

Ralph B. D'Agostino, William B. Kannel, Miganush N. Stepanians, and LeiLanie C. D'Agostino

A previously published study reported on an open-label, multicenter study of the efficacy and tolerability of lovastatin in the management of nonfamilial primary hypercholesterolemia. In the present report, results from the 213 hypercholesterolemic patients with systemic hypertension are presented. Within 1 month of lovastatin therapy (20 mg/day), the observed significant reductions in total serum cholesterol, low-density lipoprotein cholesterol and the ratio of total cholesterol to high-density lipoprotein cholesterol were, 19, 27 and 24, respectively. High-density lipoprotein cholesterol was increased by 6%. The 1-month lipid results were maintained over the full 6 months of the study. Lovastatin was generally effective in improving the serum lipids of hypercholesterolemic hypertensive patients regardless of the type of antihypertensive medications received (including diuretics and β blockers), and without changes in diastolic blood pressure. Lovastatin was generally well tolerated.

CONGESTIVE HEART FAILURE

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Effects of Cardiac Transplantation on Endothelium-Dependent Dilation of the Peripheral Vasculature in Congestive Heart Failure

Spencer H. Kubo, Thomas S. Rector, Alan J. Bank, Linda K. Tschumperlin, Leopoldo Raij, Nancy Brunsvold, and Mark D. Kraemer

This study was performed to address the hypothesis that abnormalities in endothelium-dependent vasodilation in heart failure are improved by heart transplantation. Forearm blood flow responses to the intraarterial administration of methacholine were examined in 2 separate protocols. In protocol 1, forearm blood flow responses to methacholine in 14 heart transplant recipients were significantly greater than in 10 patients with heart failure, whereas the responses to nitroprusside, an endothelium-independent vasodilator, were nearly identical in the 2 groups. In protocol 2, 6 patients were studied before and 4 months (range 1 to 11) after transplantation. Methacholine responses before transplantation were 2.5 ± 1.3, 5.2 ± 1.5 and 7.3 ± 1.5 ml/min/100 ml forearm volume and were significantly improved after transplantation to 5.7 ± 1.2, 12.1 ± 3.0 and 14.2 ± 2.2 ml/min/100 ml forearm volume (all $p < 0.05$). These data demonstrate that abnormalities in endothelium-dependent vasodilation in the peripheral vasculature in patients with heart failure are improved by heart transplantation.

MISCELLANEOUS

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Atrioventricular Conduction in Children of Women with Systemic Lupus Erythematosus

Monica Martin Goble, Macdonald Dick II, W. Joseph McCune, Janet Ellsworth,
Donita B. Sullivan, and Aaron M. Stern

To examine subtle abnormalities in atrioventricular conduction in children of women with systemic lupus erythematosus (SLE), electrocardiograms were obtained from 86 offspring of 53 women with SLE. Individual electrocardiograms showed normal sinus rhythm and atrioventricular conduction in 83 offspring. In contrast, grouped data indicated that heart rate adjusted for age was greater and PR interval adjusted for heart rate longer in offspring of mothers who had the onset of SLE before or during pregnancy than in the normal population. These observations did not hold for offspring whose mothers developed SLE after pregnancy. The findings indicate that offspring of mothers with SLE, even in the absence of bradycardia or an abnormal electrocardiogram, may have experienced a maternal internal environment that produced subclinical changes in atrioventricular conduction. However, newborns with a normal pulse rate are unlikely to have significant abnormalities in atrioventricular conduction and do not need screening electrocardiograms at birth.

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Effect of Exercise Training on Left Ventricular Performance in Older Women Free of Cardiopulmonary Disease

Robert J. Spina, Takeshi Ogawa, Tom R. Miller, Wendy M. Kohrt, and Ali A. Ehsani

Exercise training enhances left ventricular (LV) function at peak exercise in older men. To determine whether exercise training can improve LV systolic function in older women, 10 subjects (aged 60 to 79 years) completed 9 to 12 months of exercise training. Maximal oxygen uptake was increased by 21% in response to training. LV ejection fraction, end-diastolic volume, stroke volume and cardiac output did not change after training. Arteriovenous oxygen content difference at peak supine cycle ergometer exercise was increased. Thus, exercise training increases aerobic power in older women predominantly by peripheral adaptations without enhancing LV systolic performance.

METHODS

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Measurement of Cardiac Output by Automated Single-Breath Technique, and Comparison with Thermodilution and Fick Methods in Patients with Cardiac Disease

Mark R. Zenger, Matthew Brenner, Malcolm Haruno, Donald Mahon, and
Archie F. Wilson

An automated method for measuring cardiac output based on acetylene gas absorption using a single-breath constant exhalation technique was com-

Continued on page A26

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pared with standard direct Fick and thermodilution methods in patients undergoing elective cardiac or pulmonary artery catheterization. There was excellent correlation between the acetylene blood flow method and both Fick and thermodilution methods. Accurate, noninvasive measurement of cardiac output was easily obtained using the automated device, and should be useful in the evaluation of patients with cardiac disease and in monitoring the effects of therapy.

CARDIOVASCULAR PHARMACOLOGY

110

No Adaptation to Digitalization as Evaluated by Digitalis Receptor (Na,K-ATPase) Quantification in Explanted Hearts from Donors Without Heart Disease and from Digitalized Recipients with End-Stage Heart Failure

Thomas A. Schmidt, Paul D. Allen, Wilson S. Colucci, James D. Marsh, and Keld Kjeldsen

Digitalis receptor (sodium potassium adenosine triphosphatase) concentration was quantified in explanted hearts from subjects without heart disease and digitalized patients with end-stage heart failure undergoing heart transplantation. Vanadate-facilitated ^{3}H-ouabain binding to intact left ventricular samples was performed before and after clearance of previously bound digoxin by washing in buffer containing excess digoxin antibody. Digitalization was associated with an occupancy of digitalis receptors with digoxin of 24% ($p < 0.02$). After washing with antibody, the digitalis receptor concentration tended to be lower (19%, $p < 0.08$) in failing than in normal hearts. Thus, there was no evidence for adaptation to digitalization due to up-regulation of the digitalis receptor concentration when comparing the failing and the healthy human heart.

BRIEF REPORTS

115

Prognostic Significance of Silent Myocardial Ischemia in Patients >61 Years of Age With Extracranial Internal or Common Carotid Arterial Disease With and Without Previous Myocardial Infarction

Wilbert S. Aronow, Chul Ahn, Myron R. Schoenfeld, Anthony D. Mercando, and Stanley Epstein

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Ventricular Fibrillation Markers on Admission to the Hospital for Acute Myocardial Infarction

Miquel Fiol, Jaume Marrugat, Antonio Bayés, Jaume Bergadá, and Josep Guindo

Continued on page A29

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- New 100 mg vial permits convenient dosing for patients ≥65 kg with AMI or acute massive pulmonary embolism

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[1] Data on file, Genentech, Inc.

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ACTIVASE® (Alteplase)

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: Acute Myocardial Infarction: Activase® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY section of full prescribing information).

Pulmonary Embolism: Activase® is indicated in the management of acute massive pulmonary embolism (PE) in adults:

for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and

for the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, Activase® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal, surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension

WARNINGS: Bleeding: The most common complication encountered during Activase® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites. • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute to bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of Activase® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during Activase® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with Activase®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of Activase®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of Activase® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with Activase® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of Activase® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent gastrointestinal or genitourinary bleeding (within 10 days) • Recent trauma (within 10 days) • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants, e.g., warfarin sodium • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Arrhythmias: Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of Activase®, Alteplase, are administered.

Pulmonary Embolism: It should be recognized that the treatment of pulmonary embolism with Activase®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General: Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with Activase® treatment. Noncompressible arterial puncture must be avoided (i.e., internal jugular and subclavian punctures should be avoided to minimize bleeding from noncompressible sites). Arterial and venous punctures should be minimized. In the event of serious bleeding, Activase® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration: There is no experience with readministration of Activase®. If an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of Activase® has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (a single point measurement) were reported in one patient but subsequent antibody test results were negative.

Laboratory Tests: During Activase® therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Activase® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions: The interaction of Activase® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after Activase® therapy.

Use of Anticoagulants: Heparin has been administered concomitantly with and following infusions of Activase® to reduce the risk of rethrombosis. Because either heparin or Activase® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C): Animal reproduction studies have not been conducted with Activase®. It is also not known whether Activase® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Activase® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Safety and effectiveness of Activase® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of Activase® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers: It is not known whether Activase® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Activase®, Alteplase, is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding: The most frequent adverse reaction associated with Activase® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites. • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	**Total Dose > 100 mg**
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding (ICB) in patients treated with Activase® is as follows:

Dose	**Number of Patients**	**%**
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of Activase® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not significantly different in the Activase® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively)(p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, Activase® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Activase® therapy. Therefore, Activase® therapy requires careful attention to potential bleeding sites, e.g., catheter insertion sites, arterial puncture sites.

Allergic Reactions: No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions: Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of myocardial infarction and may or may not be attributable to Activase® therapy.

DOSAGE AND ADMINISTRATION: Activase® is for intravenous administration only.

Acute Myocardial Infarction: Administer Activase® as soon as possible after the onset of symptoms.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

a. The bolus dose may be prepared in one of the following ways:
   1. By removing 6 to 10 mL from the vial of reconstituted (1 mg/mL) Activase® using a syringe and needle. If this method is used with the 20 mg or 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the Activase® vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
   2. By removing 6 to 10 mL from a port (second injection site) on the infusion line after the infusion set is primed.
   3. By programming an infusion pump to deliver a 6 to 10 mL (1 mg/mL) bolus at the initiation of the infusion.

b. The remainder of the Activase® dose may be administered as follows:

   20 mg, 50 mg vials, administer using either a polyvinyl chloride bag or glass vial and infusion set.

   100 mg vials, insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted Activase®. Hang the Activase® vial from the plastic molded capping attached to the bottom of the vial.

Although the use of anticoagulants and antiplatelet drugs during and following administration of Activase® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Pulmonary Embolism: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the Activase® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

The dose may be administered using the instructions described above in Acute Myocardial Infarction (b).

A DOSE OF 150 MG OF ACTIVASE®, ALTEPLASE, SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution: Activase® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that Activase® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing Activase® 1 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because Activase® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C (36-86°F). Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

Activase® may be administered as reconstituted at 1 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass vials are acceptable. Activase® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

20 mg and 50 mg vials: Reconstitution should be carried out using a large bore needle (e.g., 18 gauge) and a syringe, directing the stream of Sterile Water for Injection, USP into the lyophilized cake. **DO NOT USE IF VACUUM IS NOT PRESENT.** Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

No other medication should be added to infusion solutions containing Activase®, Alteplase. Any unused infusion solution should be discarded.

100 mg vials: Reconstitution should be carried out using the transfer device provided, adding the contents of the accompanying 100 mL vial of Sterile Water for Injection, USP to the contents of the 100 mg vial of Activase® powder. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles. Please refer to the accompanying Instructions for Reconstitution and Administration. **100 MG VIALS DO NOT CONTAIN VACUUM.**

100 MG VIAL RECONSTITUTION

1. Use aseptic technique throughout.
2. Remove the protective flip-caps from one vial of Activase® and one vial of Sterile Water for Injection, USP (SWFI).
3. Open the package containing the transfer device by peeling the paper label off the package.
4. Remove the protective cap from one end of the transfer device and keeping the vial of SWFI upright, insert the piercing pin vertically into the center of the stopper of the vial of SWFI.
5. Remove the protective cap from the other end of the transfer device. **DO NOT INVERT THE VIAL OF SWFI.**
6. Holding the vial of Activase® upside-down, position it so that the center of the stopper is directly over the exposed piercing pin of the transfer device.
7. Push the vial of Activase® down so that the piercing pin is inserted through the center of the Activase® vial stopper.
8. Invert the two vials so that the vial of Activase® is on the bottom (upright) and the vial of SWFI is upside-down, allowing the SWFI to flow down through the transfer device. Allow the entire contents of the vial of SWFI to flow into the Activase® vial (approximately 0.5 cc of SWFI will remain in the diluent vial). Approximately two minutes are required for this procedure.
9. Remove the transfer device and the empty SWFI vial from the Activase® vial. Safely discard both the transfer device and the empty diluent vial according to institutional procedures.
10. Swirl gently to dissolve the Activase® powder. **DO NOT SHAKE.**

No other medication should be added to infusion solutions containing Activase®, Alteplase. Any unused infusion solution should be discarded.

HOW SUPPLIED: Activase® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum and in 100 mg vials without vacuum.

Each 20 mg Activase® vial (11.6 million IU) is packaged with diluent for reconstitution (20 mL Sterile Water for Injection, USP): NDC 50242-044-12.

Each 50 mg Activase® vial (29.0 million IU) is packaged with diluent for reconstitution (50 mL Sterile Water for Injection, USP): NDC 50242-044-13.

Each 100 mg Activase® vial (58 million IU) is packaged with diluent for reconstitution (100 mL Sterile Water for Injection, USP), and one transfer device: NDC 50242-085-27.

Storage: Store lyophilized Activase® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

REFERENCES: 1. Topol EJ, Morriss DC, Smalling RW, et al. A multicenter, randomized, placebo-controlled trial of a new form of intravenous recombinant tissue-type plasminogen activator (Activase®) in acute myocardial infarction. *J Am Coll Cardiol* 1987;9:1205-1213. 2. Guerci AD, Gerstenblith G, Brinker JA, et al. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. *New Engl J Med* 1987;317:1613-1618. 3. O'Rourke M, Baron D, Keogh A, et al. Limitation of myocardial infarction by early infusion of recombinant tissue-plasminogen activator. *Circulation* 1988;77:1311-1315. 4. Wilcox RG, von der Lippe G, Olsson CG, et al. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: ASSET. *Lancet* 1988;2:525-530. 5. Hampton JR, The University of Nottingham, Personal Communication. 6. Van de Werf F, Arnold AER, et al. Effect of intravenous tissue-plasminogen activator on infarct size, left ventricular function and survival in patients with acute myocardial infarction. *Br Med J* 1988;297:1374-1379. 7. National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial infarction salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. *Lancet* 1988;1:203-207. 8. Califf RM, Stump D, Thornton D, et al. Hemorrhagic complications after tissue plasminogen activator (t-PA) therapy for acute myocardial infarction. *Circulation* 1987;76:IV-1.

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G70102-R3
Revised January 1992
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Elevated Circulating Levels of Beta 2-Microglobulin in Patients with Idiopathic Dilated Cardiomyopathy

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IN CONCERT

A safety profile that works in concert with other antihypertensive agents

In limited controlled trials, no notable change in the nature or frequency of adverse reactions was shown when LOZOL was combined with other antihypertensives. LOZOL is well tolerated and does not adversely affect lipids.[1-4] And unlike Dyazide* or Maxzide,† there may be no increased risk of hyperkalemia when LOZOL is used in combination with ACE inhibitors.

ONCE A DAY
LOZOL®
INDAPAMIDE 2.5mg TABLETS
PERFORMS WITH CONFIDENCE

* Dyazide (triamterene-hydrochlorothiazide), a potassium-sparing diuretic, is a registered trademark of SmithKline Beecham Pharmaceuticals.

† Maxzide (triamterene-hydrochlorothiazide), a potassium-sparing diuretic, is a registered trademark of Lederle Laboratories.

Please see brief summary of prescribing information below.

LOZOL® (indapamide) **2.5 mg tablets**
BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical trials, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. On the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: March 1992

References: 1. Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258-262. **2. Meyer-Sabellek W,** Gotzen R, Heitz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(Suppl II):170-174. **3. Horgan JH,** O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response to indapamide. *Postgrad Med J* 1981; 57(Suppl 2):64-67. **4. Scalabrino A,** Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17-22.

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FC#93-R17 1/93

CORONARY ARTERY DISEASE

The American Journal of Cardiology

JANUARY 1, 1993, VOL. 71, NO. 1

Patency of the Infarct-Related Artery and Left Ventricular Function as the Major Determinants of Survival After Q-Wave Acute Myocardial Infarction

Marcello Galvani, MD, Filippo Ottani, MD, Donatella Ferrini, MD,
Francesco Sorbello, MD, and Franco Rusticali, MD

One hundred seventy-two patients with 1-vessel disease documented at predischarge angiography who had been followed for 43 ± 30 months after an initial Q-wave acute myocardial infarction were retrospectively evaluated to investigate the prognostic value of infarct-related artery patency and left ventricular (LV) function. Multiple logistic regression analysis revealed that only infarct artery patency (Thrombolysis in Myocardial Infarction [TIMI] grades 2–3 vs 0–1) ($Z = 2.24$; $p < 0.05$) and end-systolic volume index ($Z = -2.67$; $p < 0.01$) were independently related to survival. Sixteen cardiac deaths were observed; all 16 patients had LV dysfunction (defined as end-systolic volume index >40 ml/m^2), and 15 had an occluded infarct-related artery. In the subgroup with LV dysfunction, the 10-year percent survival rate was 20% among patients with TIMI grade 0 to 1 versus 96% with grade 2–3 ($p < 0.001$). Patency of the infarct-related artery was also the only independent predictor of recurrent ischemia ($Z = 2.59$; $p < 0.01$). In conclusion, both infarct-related artery patency and LV function are independent predictors of survival after Q-wave acute myocardial infarction. Patients with normal LV function have an excellent long-term prognosis, which is only partially counterbalanced by the tendency toward clinical instability observed in those with an open infarct-related vessel. However, when an occluded infarct-related artery is observed in the setting of LV dysfunction, the long-term outcome appears to be relatively poor.

(Am J Cardiol 1993;71:1–7)

Long-term prognostic evaluation of patients after Q-wave acute myocardial infarction (AMI) is mainly directed toward assessing the damage caused by the infarction on left ventricular (LV) function and the presence of residual ischemia.[1–6] Patency of the infarct-related artery received little attention, until it was found that pharmacologic recanalization of the infarct-related vessel improves the outcome of patients with AMI even when achieved late in the course of the necrotic process.[7,8] Patency of the infarct-related artery may influence LV remodeling[9] and provide a more stable electrophysiologic milieu[10–12]; however, it may be the hallmark of the existence of viable myocardium in the risk area favoring the recurrence of ischemic events. To assess whether the presence of residual anterograde perfusion of the infarct-related artery affects the long-term outcome of patients after Q-wave AMI, we retrospectively analyzed the prospectively collected clinical and angiographic recordings of patients with 1-vessel disease who were systematically catheterized before hospital discharge.

METHODS

Patient selection: Between January 1978 and December 1989, 1,788 patients who subsequently developed a Q-wave AMI were consecutively admitted to our coronary care unit. Of these patients, 172 fulfilled the following inclusion criteria: (1) absence of previous AMI; (2) relatively uncomplicated clinical course, i.e., absence of cardiogenic shock or severe LV heart failure (Killip class >II), or both, and no evidence of recurrent ischemia during hospital stay; (3) predischarge cardiac catheterization showing the presence of coronary artery disease limited to the infarct-related artery; and (4) absence of serious noncoronary disease that may limit long-term follow-up. Because the inclusion criteria were selected retrospectively, the clinical records of these patients were specifically reviewed to ensure that all criteria were fulfilled. At the time of hospitalization, 58 patients received intravenous thrombolytic therapy (urokinase in 28, and tissue plasminogen activator in 30), and 114 were conventionally treated.

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TABLE I Univariate Comparison Between Surviving and Nonsurviving Patients

Variable	Survivors (n = 156)	Nonsurvivors (n = 16)	p Value
Age (year)	50 ± 7	51 ± 9	0.597
% smokers	51	56	0.908
% on acetylsalicylic acid	37	44	0.806
% on β blockers	18	19	0.793
% patency of infarct-related artery	53	6	0.0001
% recurrent ischemia	21	6	0.295
% congestive heart failure	4	13	0.346
% thrombolytic therapy	35	25	0.619
Ejection fraction (%)	55 ± 12	44 ± 13	0.0006
End-diastolic volume index (ml/m^2)	100 ± 30	134 ± 36	0.0001
End-systolic volume index (ml/m^2)	46 ± 21	74 ± 23	0.00001
% left anterior descending	49	69	0.124
% left circumflex	13	0	0.265
% right coronary	38	32	0.805
% collateral flow to infarct-related artery	40	75	0.0140

Values are mean ± SD.

Electrocardiographic evaluation: Twelve-lead electrocardiograms were obtained on admission and once daily until day 8. All patients were classified as having Q-wave AMI, because their electrocardiograms showed the presence of pathologic Q waves, i.e., Q waves ≥ 30 ms in duration in ≥ 2 anterior (V_1–V_4), inferior (II, III or aVF) or lateral (V_5–V_6 or I, aVL) leads.[13]

Coronary angiography: All patients underwent selective coronary angiography and left ventriculography 10 ± 3 days after the onset of AMI. Only patients with coronary artery disease limited to the infarct-related vessel were included in the study (i.e., patients with even nonsignificant stenoses in the remaining arteries were excluded), because the presence of even nonsignificant coronary artery disease has an unfavorable effect on long-term mortality.[14]

Patency of the infarct-related artery was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) criteria.[15] Each patient was classified as having no or minimal anterograde perfusion (TIMI grades 0 and 1), or partial or complete anterograde perfusion (grades 2 or 3). LV function was evaluated in the 30° right anterior oblique projection. Ventricular volumes and ejection fraction were calculated by a single-plane area-length method.[16] Angiographically visible collaterals were graded on a 3-point scale as absent (grade 1), minimal (grade 2) or well-developed (grade 3).[17] A patient was considered to have collaterals to the infarct-related artery if the collateral perfusion grade was 2 or 3.

Clinical evaluation: Patients were regularly followed in the outpatient clinic, where detailed clinical recordings were obtained at regular intervals. During follow-up, the presence of risk factors for coronary artery disease was noted. Cardiac medications regularly received by each patient were also recorded. The occurrence of cardiac events (unstable angina, reinfarction, congestive heart failure and sudden cardiac death) was carefully evaluated.

TABLE II Univariate Comparison Between Patients With and Without Recurrent Ischemia

Variable	No Recurrent Ischemia (n = 139)	Recurrent Ischemia (n = 33)	p Value
Age (year)	51 ± 6	52 ± 8	0.423
% smokers	45	57	0.283
% on acetylsalicylic acid	41	36	0.771
% on β blockers	20	15	0.559
% patency of infarct-related artery	43	73	0.004
% survival	89	96	0.295
% congestive heart failure	4	6	0.974
% thrombolytic therapy	32	42	0.331
Ejection fraction (%)	53 ± 12	59 ± 13	0.007
End-diastolic volume index (ml/m^2)	106 ± 32	89 ± 28	0.005
End-systolic volume index (ml/m^2)	51 ± 22	38 ± 22	0.003
% left anterior descending	47	67	0.074
% left circumflex	11	15	0.689
% right coronary	42	18	0.02
% collateral flow to infarct-related artery	45	36	0.507

Values are mean ± SD.

Because the study population comprised only patients with 1-vessel disease, interventional procedures were performed only when limiting symptoms were present. No patient was lost to follow-up. Patients who underwent revascularization procedures (12 percutaneous transluminal coronary angioplasties, 11 coronary bypass surgeries and 2 left aneurysmectomies) during follow-up were recorded as alive until the date of the procedure and as lost to follow-up thereafter.

Statistical analysis: Univariate comparisons between continuous variables were performed using the unpaired *t* test and between categorical variables using the chi-square test. Independent determinants of survival and recurrent ischemia were identified using multivariate logistic regression analysis.[18] We included in the logistic regression model variables that were out of balance ($p < 0.2$) at the univariate comparison. Wald statistics were used to test the differences.[19] Survival curves were computed according to Cutler and Ederer.[20] Comparison of survival between different subgroups was performed by the method of Mantel and Haenszel.[21]

Values in the text are reported as mean ± SD. Differences were considered significant if the null hypothesis could be rejected with >95% confidence.

RESULTS

Follow-up data: The study population was followed for a mean of 43 ± 30 months (range 5 to 194). More than 50% of patients were followed for ≥3 years.

During the study period, 16 cardiac deaths were observed; 15 were sudden, and 1 was due to progressive, congestive heart failure. There were no deaths recorded of noncardiac origin. Table I shows the results of the comparison between surviving and nonsurviving patients. The former group had a higher patency rate of the infarct-related vessel and a higher ejection fraction than did the latter. Conversely, nonsurviving patients had larger diastolic and systolic volumes and showed the presence of collateral flow to the infarct-related artery more often. Among nonsurviving patients, the left anterior descending artery was the infarct-related vessel in 69% of cases versus 49% among survivors.

During follow-up, recurrent ischemia (i.e., the occurrence of unstable angina or reinfarction, or both) had an overall incidence of 19% (33 episodes among 172 patients). Table II shows the results of univariate comparison between patients with and without recurrent ischemia during the study period. Patients with recurrent ischemic events had a significantly higher patency rate of the infarct-related artery and had better LV function than did subjects without those events. Lesions of the right coronary artery were particularly infrequent among patients with recurrent ischemia. Furthermore, survival was similar between the 2 patient groups, possibly because all patients with unstable angina (19 of 33) underwent successful revascularization procedures.

Analysis of survival: Figure 1 shows the results of multiple logistic regression analysis applied to survival as the dependent variable. End-diastolic volume index, ejection fraction, left anterior descending as the infarct-related artery, and presence of collateral flow to the infarct-related vessel were not found to have an independent prognostic value. Survival was most significantly related to patency of the infarct-related artery ($p < 0.05$) and to end-systolic volume index ($p < 0.01$).

According to the patency status of the infarct-related artery, 88 patients were found to have TIMI grade 0–1, whereas 84 had grade 2–3 (8 with grade 2, and 76 with grade 3). The overall 10-year mortality rate was 9%. Only 1 patient with TIMI grade 2–3 of the infarct-related artery died during follow-up. Conversely, the remaining 15 nonsurviving patients had TIMI grade 0–1. Therefore, the 10-year percent survival rates were 98% in

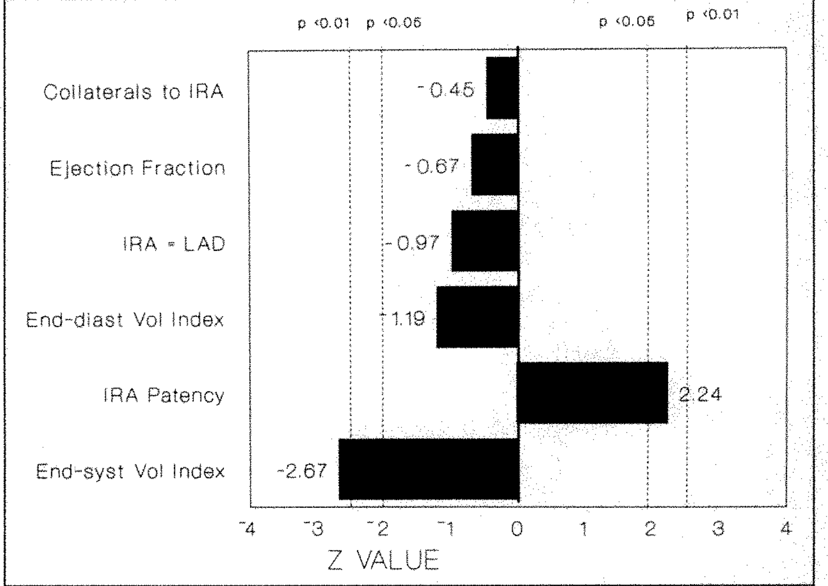

FIGURE 1. Results of multiple logistic regression analysis applied to survival as dependent variable. Among 6 univariate predictors of survival, only patency of infarct-related artery (IRA) (p <0.05) and end-systolic volume (End-syst Vol) index (p <0.01) were independently related to occurrence of fatal cardiac events. End-diast Vol = end-diastolic volume; LAD = left anterior descending artery.

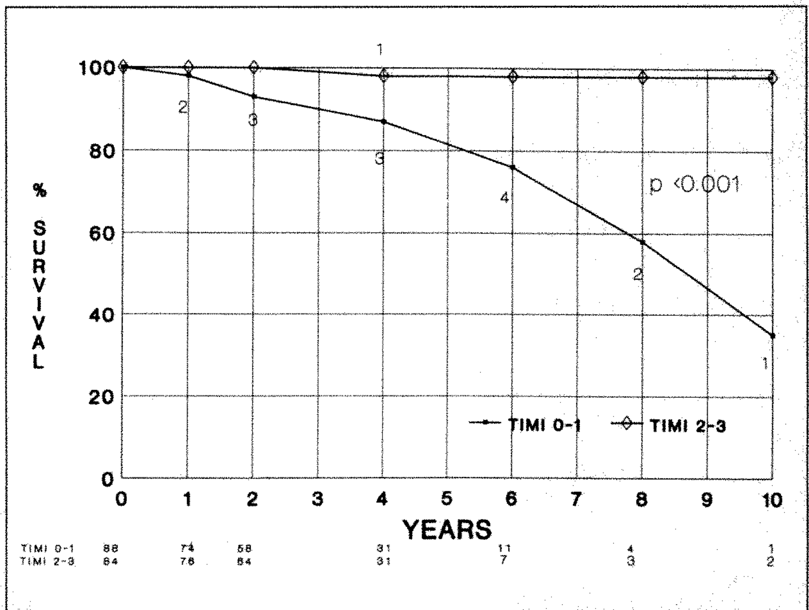

FIGURE 2. Life-table survival analysis for Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 and 2–3 patient groups. Over 10 years of observation, TIMI patients grade 2–3 had significantly better survival rate than did grade 0–1 subjects. Number of deaths recorded at each follow-up interval in each group is shown in *diagram.* Number of patients at beginning of each follow-up interval in corresponding groups is shown at *bottom of graph.*

patients with TIMI grade 2–3 and 33% in those with grade 0–1. This difference was highly significant (p <0.001) (Figure 2).

According to the presence of LV dysfunction (defined as end-systolic volume index exceeding the upper limit of normal for our laboratory, i.e., >40 ml/m^2), 98 patients had enlarged end-systolic volume indexes and 74 did not. Although slightly higher among patients with TIMI grade 0–1, end-systolic volume indexes were not significantly different between those with and without anterograde perfusion of the infarct-related artery. No deaths were recorded in patients with end-systolic volumes <40 ml/m^2. Among patients with LV dysfunction, mortality was 30% (15 of 51) in those with TIMI grade

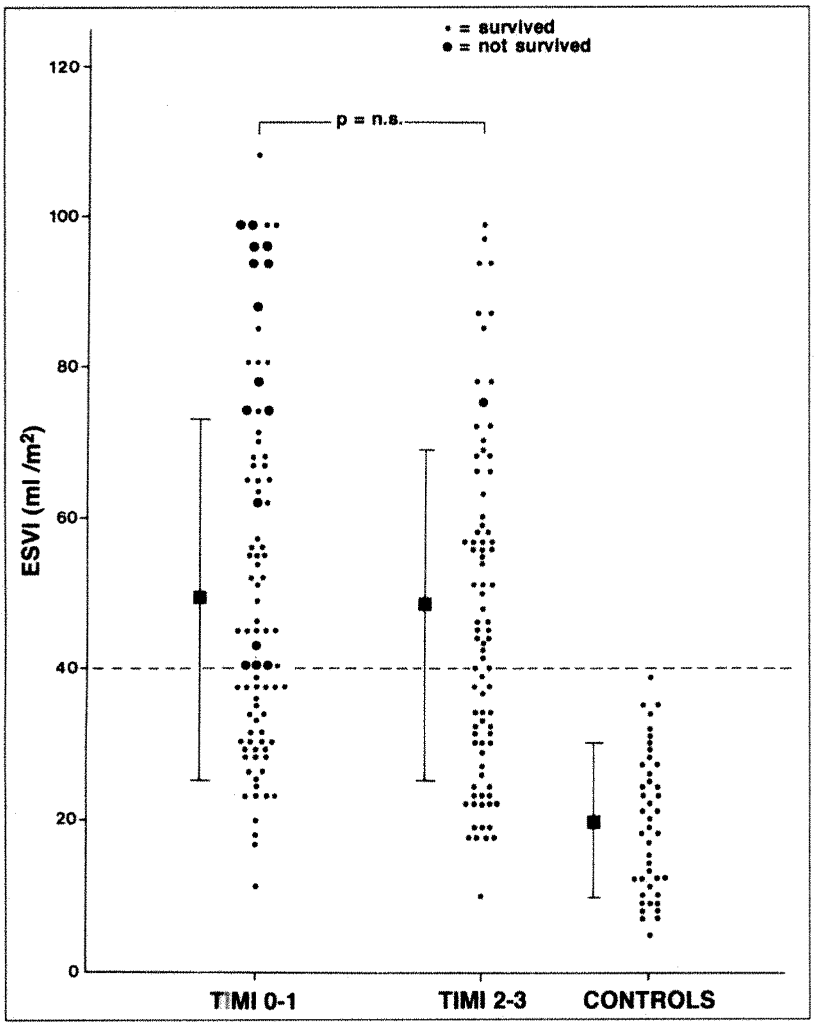

FIGURE 3. Relation between patency of infarct-related artery and left ventricular (LV) dysfunction. Survivors are indicated by *small circles*, and patients who died by *large circles*. *Right*, end-systolic volume indexes (ESVI) of 43 control subjects are shown. *Dotted line* represents upper limit of normality (i.e., mean + 2 SD) of ESVI used to separate patients with and without LV dysfunction: 40 ml/m^2. ESVIs were similar among Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 and 2–3 patients. Mortality was 0% in patients without LV dysfunction, 2% in those with LV dysfunction and patent infarct-related artery, and 30% in those with LV dysfunction and no anterograde perfusion of infarct-related vessel. n.s. = not significant.

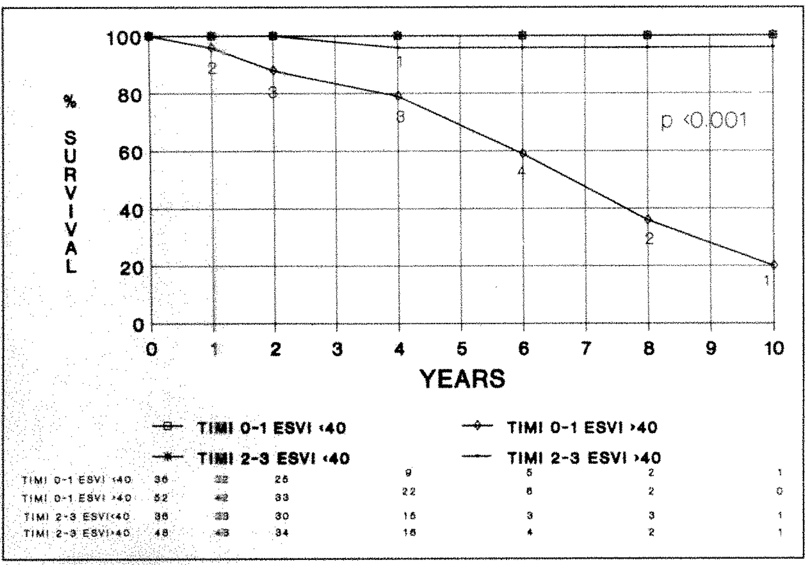

FIGURE 4. Life-table survival analysis for Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 and 2–3 patients according to presence of left ventricular (LV) dysfunction (end-systolic volume index [ESVI] >40 ml/m^2). Over 10 years of observation, TIMI grade 0–1 patients with LV dysfunction had the worst clinical outcome (p <0.001 vs grade 0–1 with ESVI <40 ml/m^2 and grade 2–3 with ESVI >40 ml/m^2).

0–1 versus 2% in those with grade 2–3 (Figure 3). Figure 4 shows the effects of infarct-related artery patency and LV dysfunction on long-term survival. Because no deaths were observed in patients without LV dysfunction, the 10-year survival rate was 100% in patients with both TIMI grades 0–1 and 2–3. Among patients with end-systolic volume index >40 ml/m^2, the percent survival rate at the end of follow-up was 96% in those with patent infarct-related arteries versus 20% in those with closed arteries ($p < 0.001$). Patients with TIMI grades 0–1 and 2–3 had similar ejection fractions (53 ± 13% vs 54 ± 11%), end-diastolic volume indexes (106 ± 30 vs 100 ± 35 ml/m^2), incidence of left anterior descending artery as the culprit vessel (52 vs 52%), and follow-up durations (42 ± 33 vs 44 ± 27 months).

Analysis of recurrent ischemia: Figure 5 shows the results of multiple logistic regression analysis applied to recurrent ischemia as the dependent variable. Only the patency of the infarct-related artery appeared to be an independent predictor of recurrent ischemia in the study population ($p < 0.01$). The incidence of recurrent ischemia during follow-up according to patency of the infarct-related vessel is shown in Figure 6. Nine episodes of recurrent ischemia occurred in patients with TIMI grade 0–1, and 24 in those with grade 2–3. Most events were observed during the first year (52%) and occurred only in patients with patent infarct-related arteries. After 10 years, only 55% of patients with TIMI grade 2–3 were free from recurrent ischemia versus 80% of those with grade 0–1 ($p < 0.01$).

Effects of thrombolysis: Thrombolytic therapy was given to 33% of the study population. In these patients, the time elapsed between admission and cardiac catheterization was similar to that observed in conventionally treated subjects (10 ± 3 vs 9 ± 4 days). Because of historical reasons, follow-up duration was significantly shorter in the thrombolysis group (36 ± 12 vs 67 ± 16 months; $p < 0.01$). When compared with the conventionally treated group, patients given thrombolysis were more likely to have recurrent ischemia during follow-up

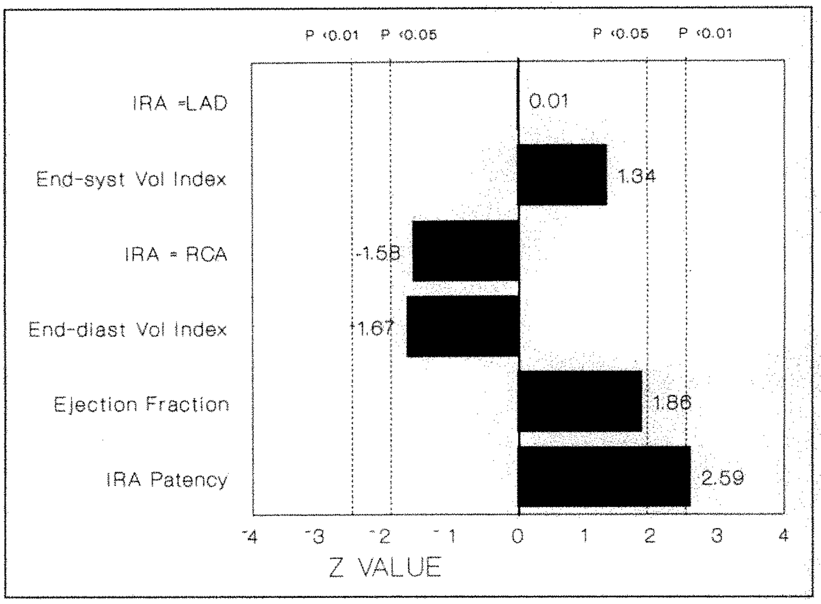

FIGURE 5. Results of multiple logistic regression analysis applied to recurrent ischemia (occurrence of unstable angina or reinfarction, or both, during follow-up) as dependent variable. Among 6 significantly different variables between patients with and without recurrent ischemia at univariate comparison, only patency of infarct-related artery (IRA) was shown to have independent value. RCA = right coronary artery; other abbreviations as in Figure 1.

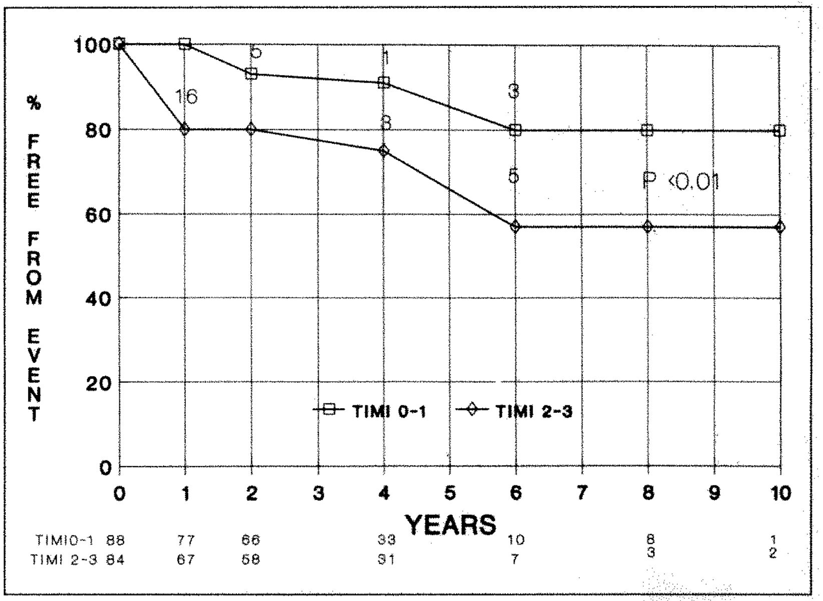

FIGURE 6. Event-free rate from recurrent ischemia in Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 and 2–3 patients. Over 10 years of observation, TIMI grade 2–3 patients had a higher rate of recurrent ischemia than did grade 0–1 subjects (p <0.01). Number of events observed in each group at each follow-up interval is indicated in *diagram*. Number of patients in each group at beginning of each follow-up interval is shown at *bottom of graph*.

TABLE III Mortality with Respect to Patency Status of Infarct-Related Artery in Published Studies

Study	No. of Pts.	Treatment	Time to Angio	Mean FU (mos)	% Cumulative Mortality	
					No IRA Pat.	IRA Pat.
Trappe et al[25]	160	Conv	Not stated	50	21	9
Gohlke et al[24]*	102	Not stated	< 1 year	51	17	13
Dalen et al[26]	289	Thromb.	90 min	12	15	8
Cigarroa et al[23]	179	Conv./thromb.	1–150 days	47	18	0
Present study	172	Conv./thromb.	4–14 days	43	17	1

*Left anterior descending lesions only, proximal to first septal perforator.

Angio = angiography; Conv. = conventional; FU = follow-up; IRA = infarct-related artery; Pat. = patency; Thromb. = thrombolysis.

(24 vs 17%), and a higher patency rate of the infarct-related artery (57 vs 45%), but similar LV function (end-diastolic volume index 104 ± 35 vs 103 ± 31 ml/m^2, end-systolic volume index 49 ± 24 vs 49 ± 22 ml/m^2, and ejection fraction 55 ± 10% vs 53 ± 13%). However, among patients with patent infarct-related arteries, LV function was significantly better in patients treated with thrombolysis than in conventionally treated subjects (end-diastolic volume index 94 ± 32 vs 116 ± 36 ml/m^2, $p < 0.01$; end-systolic volume index 42 ± 21 vs 56 ± 27 ml/m^2, $p < 0.05$; and ejection fraction 56 ± 10% vs 53 ± 10%, p = NS). No differences were observed in the group with occluded infarct-related vessels.

DISCUSSION

The results of this study indicate that among short-term surviving patients of Q-wave AMI, the long-term clinical outcome of those with patent infarct-related arteries is more benign than that observed in those without anterograde perfusion. To avoid biases that occur due to patients undergoing angiographic study at different times after the acute event (often on the basis of clinical indications), we included only those who underwent routine predischarge angiography. Furthermore, to rule out the potentially confounding effects of multivessel disease on survival,[22] only patients with coronary artery disease limited to the infarct-related artery were selected. In this study population, cardiac death was relatively infrequent (overall mortality rate 9%), mainly sudden and almost invariably associated with LV dysfunction and absence of anterograde perfusion in the infarct-related artery. All 16 patients who died had an increased end-systolic volume, and 94% (n = 15) had no or minimal anterograde flow.

The importance of LV end-systolic volume as the major determinant of late outcome has been emphasized by White et al[6] and also has been uniformly confirmed in subsequent studies.[23] Patency of the infarct-related artery was the second predictor of mortality in our study population. The results are in agreement with those reported in the 4 previous studies that examined the prognostic impact of the patent artery on survival[23–26] (Table III). All these studies consistently indicated that vessel patency is associated with a better clinical outcome.

The relative prognostic importance of LV dysfunction and patency of the infarct-related artery is an unresolved issue. We and other investigators[23] have found that patients with and without vessel patency have similar LV volumes and function. However, both LV dysfunction and patency status of the infarct-related artery may have a causal relation with the pathogenetic mechanism underlying the death of post–Q-wave AMI patients. This presumptive evidence is supported by the consistent observation that the vast majority of deaths, both in our study and in others,[6,23,25] was sudden, thus involving ventricular fibrillation as the terminal event.

Another important point is whether vessel patency is associated with better LV function. In this respect, our predischarge catheterization data are in contrast with those of Schroder et al[27] who reported the angiographic findings obtained 1 month after AMI in the Intravenous Streptokinase in Acute Myocardial Infarction study subgroup of patients without noninvasive evidence of early reperfusion. In that study, a patent infarct-related artery was associated with better LV function, regardless of whether patients were treated with the thrombolytic agent. Because functional recovery of the ischemic myocardium after coronary occlusion may be variable and can take several days,[28] it is conceivable that predischarge angiography may obscure the difference between patients with and without a patent artery, because of myocardial stunning still present at the time of the invasive study.

Our study also indicates that recurrent ischemia occurs very frequently among post–Q-wave AMI patients with patent coronary arteries, particularly in the first year after the acute event. The pathophysiologic basis of this clinical instability may be the presence of residual jeopardized myocardium within the perfusion zone of the infarct-related vessel, as has been shown in patients with non–Q-wave AMI.[29] Accordingly, patients with recurrent ischemia had better LV function than did those without it (Table II).

The main limitation of this study is that we evaluated a mixed study population (i.e., subjects treated or not treated with intravenous thrombolysis). However, this does not appear to have affected the results of the study, because time to angiography was similar in the 2 patient groups, both groups had no evidence of recurrent ischemia during the hospital stay, and thrombolytic therapy had no independent influence on survival and recurrent ischemia, as ascertained by multiple logistic regression analysis.

In conclusion, the results of this study indicate that in patients with 1-vessel disease surviving an initial Q-wave AMI, the occurrence of fatal events during follow-up can be reliably predicted by the patency status of the infarct-related artery and by the presence or absence of LV dysfunction. The finding of normal end-systolic volume with or without patency of the infarct-related artery identifies a group of subjects with an excellent long-term prognosis. Among these subjects, those with preserved anterograde perfusion of the infarct-related artery have a high incidence of nonfatal recurrent ischemic events, possibly linked to the presence of viable myocardium in the risk area supplied by the culprit vessel. However, the association of LV dysfunction and an occluded infarct-related vessel appears to be a high-risk combination that has the potential for substantial late mortality (cumulative rate 30%).

Acknowledgment: We thank Harvey D. White, MB, ChB, FRCP, for helpful criticism. We are also grateful for the expert assistance of Jean Ellen Page in preparing the manuscript.

REFERENCES

1. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331–336.
2. Rapaport E, Remedios P. The high risk patient after recovery from myocardial infarction: recognition and management. *J Am Coll Cardiol* 1983;1:391–400.
3. Taylor GJ, Humphreis JO, Mellits ED, Pitt B, Schulze RA, Griffith LSC, Achuff SC. Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. *Circulation* 1980;62:960–970.
4. Norris RM, Barnaby PF, Brandt PWT, Geary GG, Whitlock RML, Wild CJ, Barratt-Boyes BG. Prognosis after recovery from first myocardial infarction: determinants of reinfarction and sudden death. *Am J Cardiol* 1984;53:408–413.
5. Madsen EB, Hougaard P, Gilpin E. Dynamic evaluation of prognosis from time-dependent variables in acute myocardial infarction. *Am J Cardiol* 1983;51:1579–1583.
6. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;76:44–51.
7. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349–360.
8. Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz J. The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12-month follow-up report. *N Engl J Med* 1985;312:1073–1078.
9. Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular thrombus formation after first anterior wall acute myocardial infarction. *Am J Cardiol* 1988;62:31–35.
10. Sager PT, Perlmutter RA, Rosenfeld LE, McPherson CA, Wackers FJT. Electrophysiologic effects of thrombolytic therapy in patients with a transmural anterior myocardial infarction complicated by left ventricular aneurysm formation. *J Am Coll Cardiol* 1988;12:19–24.
11. Kersshot IE, Brugada P, Ramentol M, Zehender M, Waldecker B, Stevenson WG, Geibel A, Dezwaan C, Wellens HJJ. Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation: a prospective, randomized study. *J Am Coll Cardiol* 1986;7:1234–1242.
12. Gang ES, Lew AS, Hong M, Wang FZ, Siebert CA, Peter T. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1989;321:712–716.
13. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Boston: John Wright-PSG, 1982.
14. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL, and Participants in the Coronary Artery Surgery Study. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol* 1986;7:479–483.
15. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;76:142–154.
16. Wynne J, Green LH, Mann T, Levin D, Grossman W. Estimation of left ventricular volumes in man from biplane cineangiograms filmed in oblique projections. *Am J Cardiol* 1978;41:726–731.
17. Habib GB, Heibig J, Forman SA, Brown BG, Roberts R, Terrin ML, Bolli R, and the TIMI Investigators. Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I Thrombolysis in Myocardial Infarction (TIMI) trial. *Circulation* 1991;83:739–746.
18. Schlesselman JJ. Case Control Studies: Design, Conduct, Analysis. Oxford, United Kingdom: University Press, 1982:227–269.
19. Shurtleff D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 18 year follow-up. In: The Framingham Study, an Epidemiological Investigation of Cardiovascular Disease. London: Gordon and Kannel Editors, 1981:241–248.
20. Cutler S, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chron Dis* 1958;8:699–722.
21. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–723.
22. Sanz G, Castaner A, Betriu A, Magriña J, Roig E, Coll S, Paré JC, Navarro-Lopez F. Determinants of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. *N Engl J Med* 1982;306:1065–1070.
23. Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. *Am J Cardiol* 1989;64:155–160.
24. Gohlke H, Heim E, Roskamm H. Prognostic importance of collateral flow and residual coronary stenosis of the myocardial infarct artery after anterior wall Q-wave acute myocardial infarction. *Am J Cardiol* 1991;67:1165–1169.
25. Trappe HJ, Lichtlen PR, Klein H, Wenzlaff P, Harrtwig CA. Natural history of single vessel disease. Risk of sudden coronary death in relation to coronary anatomy and arrhythmia profile. *Eur Heart J* 1989;10:514–524.
26. Dalen JE, Gore JM, Braunwald E, Borer J, Goldberg RJ, Passamani ER, Forman S, Knatterud G, and the TIMI Investigators. Six- and twelve-month follow-up of the phase I Thrombolysis in Myocardial Infarction (TIMI) trial. *Am J Cardiol* 1988;62:179–185.
27. Schroder R, Neuhaus KL, Linderer T, Bruggemann T, Tebbe U, Wegscheider K. Impact of late coronary artery reperfusion on left ventricular function one month after acute myocardial infarction (results from the ISAM study). *Am J Cardiol* 1989;64:878–884.
28. Braunwald E, Kloner RA. The stunned myocardium: prolonged postischemic ventricular dysfunction. *Circulation* 1982;66:1146–1149.
29. Gibson RS, Beller GA, Gheorghiade M, Nygaard TW, Watson DD, Huey BL, Sayre SL, Kaiser DL. The prevalence and clinical significance of residual myocardial ischemia two weeks after uncomplicated non-Q-wave infarction: a prospective natural history study. *Circulation* 1986;73:1186–1198.

Comparison in Acute Myocardial Infarction of Anisoylated Plasminogen Streptokinase Activator Complex Versus Heparin Evaluated by Simultaneous Thallium-201/Technetium-99m Pyrophosphate Tomography

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In a subgroup of 45 patients with acute myocardial infarction (AMI) from the German multicenter trial of anisoylated plasminogen streptokinase activator complex (APSAC) (n = 20) versus heparin (n = 25), simultaneous thallium (Tl)-201 technetium (Tc)-99m pyrophosphate (PYP) tomography was initiated to elucidate a possible benefit of APSAC over heparin. Findings in the 2 treatment groups were similar with respect to Tl-201 defect score, relative scintigraphic infarct size, and in keeping with the main group coronary artery patency, global ejection fraction and maximal creatine kinase level. However, 2 different Tl-201/Tc-99m PYP accumulation patterns within the area of infarction (homogeneous, group A; inhomogeneous, group B) were identified. Both treatment groups were similar with regard to the frequency of the homogeneous and inhomogeneous pattern. In comparing the 2 accumulation patterns, creatine kinase peaked earlier in group A than in group B, and global left ventricular ejection fraction was significantly higher in group A than in group B. In Group A, 30 of 31 patients and in group B 7 of 11 patients had a patent infarct-related vessel ($p < 0.025$). Tl-201 defect score was lower in group A than in group B. Likewise, relative size of the infarction as determined from Tc-99m PYP images was significantly lower in group A than in group B. Fifteen patients experienced cardiogenic shock or severe heart failure. Patients in group B had a higher incidence of these in-hospital complications than patients in group A (92 vs 12%, $p < 0.0005$). Scintigraphic infarct size and Tl-201 defect score were greater in patients with the aforementioned clinical events. In addition to scintigraphic infarct size and coronary patency, the Tl-201/Tc-99m PYP accumulation pattern was useful in differentiating patients with from those without an adverse clinical course.

It is concluded that Tl-201/Tc-99m PYP tomography is a promising tool for evaluating AMI and predicting the clinical course of patients.

(Am J Cardiol 1993;71:8–13)

Radionuclide studies are frequently used to evaluate patients with acute myocardial infarction (AMI) undergoing thrombolytic therapy. Myocardial salvage can be assessed using serial examinations after either intravenous or intracoronary thallium-201 (Tl-201) application.[1,2] Some studies suggested early technetium pyrophosphate (Tc-99m PYP) uptake as a marker of reperfusion.[3,4] Only few investigators performed dual radioisotope studies using a marker for perfusion and a marker for necrosis simultaneously.[5–9] Hashimoto et al[7] demonstrated that Tl-201/Tc-99m PYP overlap on dual emission computed tomography can differentiate early reperfusion from slightly delayed recanalization. With use of combined simultaneous Tl-201/Tc-99m PYP tomography, the present randomized study was undertaken (1) to elucidate a possible benefit of anisoylated plasminogen streptokinase activator complex (APSAC) over heparin, (2) to relate different Tl-201/Tc-99m accumulation patterns to clinical findings, and (3) to test the feasibility of dual radioisotope tomography for predicting the clinical course of patients after AMI.

METHODS

The study group comprised 45 of 55 consecutive patients with AMI admitted to the intensive care unit of the medical department, University of Freiburg. These patients were part of the German multicenter trial of APSAC versus heparin which was published recently.[10] Ten patients could not be examined by scintigraphy for logistic reasons. Patients were included in the study when they had ≥30 minutes of chest pain and ST-segment elevation of ≥0.1 mV in at least 1 standard electrocardiographic lead and ≥0.2 mV in at least 1 V lead persisting even after sublingual administration of either 0.8 mg nitroglycerin or 10 mg nifedipine. Patients with contraindications to fibrinolytic therapy, as well as patients in cardiogenic shock, were excluded from the study. Additional exclusion criteria were chest pain lasting for >4 hours before presentation and ST-segment

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elevation in the presence of Q waves, indicating previous infarction.

Study protocol: Methylprednisolone (100 mg) was given to both groups intravenously before treatment. Immediately after randomization, either 30 U of APSAC as an intravenous injection over 5 minutes, or 5,000 U of heparin followed by an infusion of 17 U/kg/hour was given. In the APSAC group, heparin infusion was also begun 4 hours after the administration of APSAC. Heparin treatment was continued until cardiac catheterization was performed 14 to 21 days later. Care was taken to adjust the partial thromboplastin time to 1.5 to 2 times normal. Cardioactive drug treatment was given, if clinically indicated, at the discretion of the attending physician.

Myocardial imaging: Simultaneous Tl-201/Tc-99m PYP tomography was performed within 4 days after the onset of chest pain. All patients were examined during a stable phase of ≥12 hours after AMI. Tomography was obtained using the 7 pinhole technique in an approximately 40° left anterior oblique, 10° cephalad tilt projection. Scintigrams were recorded using a 38 cm large field-of-view camera (Dyna 4, Picker) with 2 impulse height analyzers. A commercial 7-pinhole collimator focused at 13.5 cm with seven 5.3 mm pinholes was fitted to the camera. Energy discrimination was provided by a 15% window centered on the 75 keV peak for Tl-201 and a 5% window centered on 140 keV for Tc-99m. This adjustment yields optimal results, as shown in a previous study.[11] The imaging time ranged between 12 and 17 minutes.

Scatter corrections: The raw data were corrected for down-scattered Tc-99m counts and for radioactivity from Tl-201 gamma rays (135 and 167 keV) according to the following formulas, as reported[12]: $a = A - B\alpha$; $b = B - A\beta$ (a = corrected Tl-201 counts; A = total sample counts at 75 keV; α = Tc-99m standard at 75 keV/Tc-99m standard at 140 keV; b = corrected Tc-99m counts; B = total sample counts at 140 keV; β = Tl-201 standard at 140 keV/Tl-201 standard at 75 keV).

Data processing and overlay technique: Tl-201 and Tc-99m PYP tomograms were separately reconstructed according to the method employed by Vogel et al.[13] Sixteen slices of nominal 0.8 cm intervals were generated. After reconstruction, images were viewed using a 15- step color scale. For dual isotope display, the Tc-99m PYP images were background-subtracted to ensure that residual blood pool activity of Tc-99m PYP could no longer be seen. Then the images were inversely colored and overlaid on the normally-colored and background-subtracted Tl-201 images.

Image analysis: The first 6 short-axis slices following the apex were used for evaluation. Tl-201 defects or Tc-99m PYP accumulations had to be present on ≥2 contiguous slices. A Tl-201 defect was diagnosed if the regional viability index as defined by Stirner et al[14] was below 75%. In the Tl-201/Tc-99m PYP tomograms, every accumulation with greater intensity than residual blood pool activity localized in the ventricular wall was judged pathologic, as previously described.[15]

From each Tl-201/Tc-99m PYP tomogram, the angle α under which the Tc-99m PYP accumulation appeared was measured for each short-axis slice and expressed in degrees. Relative infarct size (in degrees) was defined as mean value of the 6 slices. Accordingly, a Tl-201 defect score (in arbitrary units) was calculated from areas of moderately reduced Tl-201 uptake (MRU: 45% ≤ VI ≤ 75%) or extensively reduced uptake (ERU: VI <45%) using the following formula:

$$\text{Score}_{\text{Tl}} = \sum_{n=1}^{6} \frac{\text{MRU} + 1/2 \cdot \text{ERU}}{6}$$

Tl-201/Tc-99m pyrophosphate accumulation patterns: Additional analyses were based on 2 different Tl-201/Tc-99m PYP accumulation patterns that could be identified (Figure 1): (1) intense and homogeneous Tc-99m PYP accumulation corresponding to a Tl-201 defect (group A); and (2) inhomogeneous Tc-99m PYP accumulation within the Tl-201 defect (group B). In group B, the maximal activity was predominantly localized in the infarct periphery with relatively less or no pathologic central uptake.

Cineventriculography: Of the 45 patients, 42 had high-quality simultaneous biplane coronary angiography and underwent left-sided cardiac catheterization within 2 to 3 weeks after AMI.

Creatine kinase: Blood samples for determination of creatine kinase level were collected every 3 hours for up to 24 hours after the start of treatment and every 6 hours for the next 48 hours as a noninvasive measure to judge early reperfusion. Patients with a creatine kinase peak ≤ 15 hours were regarded as having early reperfusion.[16]

Statistical analysis: Values reported are mean value ± 1 SD. Comparisons between groups were obtained with the Wilcoxon test. The chi-square test or Fisher's exact test was used in the clinical course comparison.

RESULTS

Of the 45 patients, 20 received APSAC and 25 heparin. Every patient showed a Tl-201 defect and a corresponding Tc-99m PYP accumulation. Thirty-three patients (73%) had a homogeneous (group A) and 12 patients (27%) an inhomogeneous (group B) Tc-99m PYP accumulation pattern in the area of a Tl-201 defect.

APSAC versus heparin: Analysis of the clinical data revealed no significant difference between the APSAC and the heparin groups with respect to sex, mean age, infarct location, time from AMI to treatment and time to scintigraphy (Table I). With regard to the Tl-201/Tc-99m PYP pattern, no significant difference was seen between the APSAC group (group A: n = 15; group B: n = 5), and the heparin group (group A: n = 18; group B: n = 7) (Table II). Moreover, scintigraphic infarct size, Tl-201 defect score, global ejection fraction, late patency of the infarct-related vessel, and maximal creatine kinase level were comparable in both groups, whereas creatine kinase in the APSAC group peaked after 11 ± 6 hours and thus was seen significantly (p <0.001) earlier than in the heparin group with a creatine kinase peak after 19 ± 7 hours (Table II).

Tl-201/Tc-99m pyrophosphate uptake pattern: Baseline characteristics in patients with a homogeneous Tl-

201/Tc- 99m PYP pattern (group A) were not different from those with an inhomogeneous pattern (group B) (Table III). Additionally, maximal increase in creatine kinase was similar in both groups. However, creatine kinase peaked earlier in group A than in group B (Table IV). Moreover, global left ventricular ejection fraction was significantly higher in group A than in group B (Table IV).

In Group A, 30 of 31 patients had a patent infarct-related coronary artery. One patient with occlusion of the left anterior descending coronary artery showed complete filling of the infarct vessel by collaterals. In group B, 7 of 11 patients had a patent infarct-related vessel (Table IV). Filling over collaterals was not seen in group B patients with persistently occluded infarct vessels.

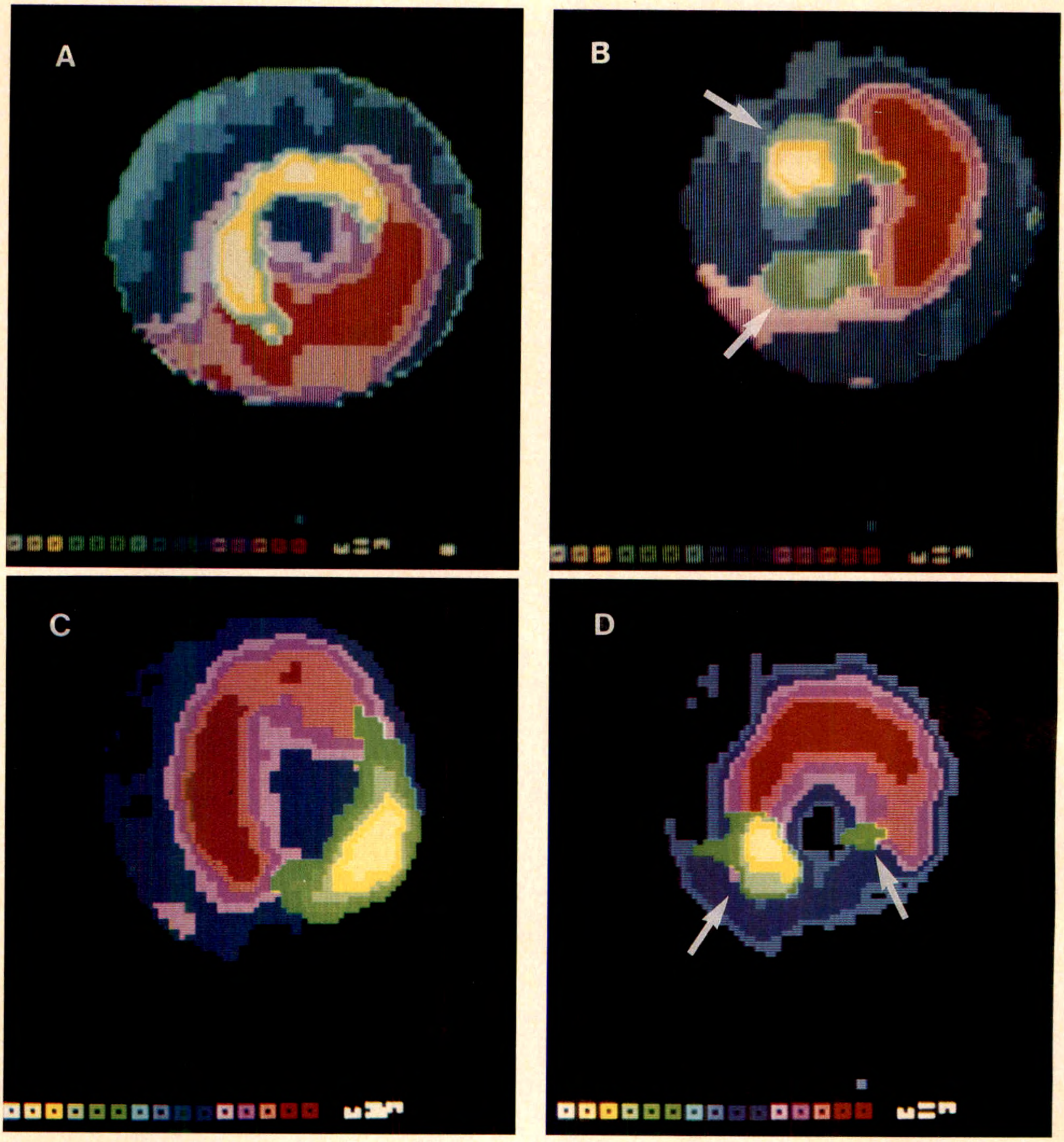

FIGURE 1. Homogeneous *(A and C)* versus inhomogeneous *(B and D)* technetium-99m pyrophosphate (Tc-99m PYP) accumulation in acute myocardial infarction indicating low or high risk of developing severe heart failure: short-axis cuts of thallium (Tl)-201/Tc-99m PYP tomography in 4 different patients. Normal Tl-201 accumulation is shown in *red,* Tl-201 defect in *blue,* and Tc-99m PYP uptake in *yellow and green. A,* homogeneous Tc-99m PYP accumulation corresponding to a Tl-201 defect is seen in anteroseptal infarction; *B,* inhomogeneous Tc-99m PYP accumulation *(arrows)* is located at the edge of the corresponding Tl-201 defect in anteroseptal infarction; *C,* homogeneous Tc-99m PYP accumulation corresponding to Tl-201 defect is seen in posterolateral infarction; *D,* inhomogeneous Tc-99m PYP accumulation *(arrows)* is located at the edge of the corresponding Tl-201 defect in inferior infarction.

TABLE I Baseline Characteristics of Treatment Groups

Patient Characteristics	APSAC (n = 20)	Heparin (n = 25)
Age (years)	57 ± 8	56 ± 9
Men/women	15/5	20/5
Infarct location		
Anterior	11	11
Inferior	9	14
Time to treatment (min)	175 ± 38	161 ± 56
Time to scintigraphy (hours)	28 ± 12	33 ± 19

APSAC = anisoylated plasminogen streptokinase activtor complex.

TABLE II Comparison of 20 APSAC Patients and 25 Heparin Patients

	APSAC (n = 20)	Heparin (n = 25)	p Value
Tl-201/Tc-99m PYP pattern			
Homogeneous (group A)	15	18	
Inhomogeneous (group B)	5	7	NS
Tl-201 defect score	137 ± 88 U	183 ± 106 U	NS
Tc-99m PYP infarct size	135 ± 78°	143 ± 45°	NS
Global LVEF	57 ± 17	55 ± 15	NS
Patency of the culprit vessel (n = 42)	17/19 (89%)	20/23 (87%)	NS
Max CK	925 ± 507 U/L	1,025 ± 659 U/L	NS
Time to CK peak	11 ± 6 hours	19 ± 7 hours	<0.001

APSAC = anisoylated plasminogen streptokinase activator complex; CK = creatine kinase; LVEF = left ventricular ejection fraction; Max. = maximal; PYP = pyrophosphate; Tc = technetium; Tl = thallium; U = arbitrary units.

TABLE III Baseline Characteristics of Groups A and B

	Tl-201/Tc-99m PYP Pattern	
Patient Characteristics	Homogeneous (group A) (n = 33)	Inhomogeneous (group B) n = 12)
Age (years)	57 ± 8	56 ± 9
Men/women	27/6	8/4
Infarct location		
Anterior	15	7
Inferior	18	5
Time to treatment (min)	162 ± 39	165 ± 64
Time to scintigraphy (hours)	31 ± 20	27 ± 12

Abbreviations as in Table II.

TABLE IV Comparison of Homogeneous (group A) and Inhomogeneous (group B) Tl-201/Tc-99m PYP Accumulation Patterns

	Group A (n = 33)	Group B (n = 12)	p Value
Tl-201 defect score	132 ± 89 U	242 ± 98 U	<0.005
Tc-99m PYP infarct size	121 ± 72°	188 ± 74°	<0.05
Global LVEF	60 ± 13%	46 ± 14%	<0.005
Max CK	941 ± 617 U/L	1,097 ± 523 U/L	NS
Time to CK peak	15 ± 8 hours	18 ± 7 hours	<0.05
Patency of the culprit vessel (n = 42)	30/31 97%	7/11 64%	<0.025

Abbreviations as in Table II.

With regard to Tl-201/Tc-99m PYP accumulation pattern, the Tl-201 defect score was lower in group A than in group B. Likewise, relative size of the infarction as determined from Tc-99m PYP images was significantly lower in group A than in group B (Table IV).

Clinical course: A total of 15 patients experienced cardiogenic shock or severe heart failure. Patients in group B had a higher incidence of these in-hospital complications compared with patients in group A (92 vs 12%, $p < 0.0005$) (Figure 2). Two patients in group B died of cardiogenic shock.

Tl-201 defect score and scintigraphic infarct sizes were greater in patients with the above-mentioned clinical events (Tl-201: 229 ± 87 vs 128 ± 97 U, $p < 0.01$; Tc-99m PYP: 193 ± 65° vs 112 ± 79°; $p < 0.05$).

Other complications included arrhythmia in 18 patients, infarct extension by routine clinical criteria in 4 patients, and atrioventricular block in 3 patients. However, no correlation with the Tl-201/Tc-99m accumulation pattern was seen in these patients.

DISCUSSION

APSAC versus heparin: The first purpose of this study was to assess noninvasively a possible benefit of APSAC over heparin by Tl-201/Tc-99m PYP tomography. The recently published German multicenter trial of APSAC versus heparin for AMI[10] as well as other reports[17–19] demonstrated the favorable influence of APSAC on clinical course in the hospital. However, in contrast to other published reports,[19,20] no differences were found in the German multicenter trial between the 2 treatment groups regarding coronary artery patency assessed by late angiography and left ventricular ejection fraction. The subgroup of the present study examined by scintigraphy showed similar results. In agreement with the clinical and angiographic data, scintigraphic findings corresponded in both treatment groups. Other reports have described a significant reduction in infarct size (up to 31%) in the APSAC group.[19,20] However, these studies also showed significant differences with respect to frequency of reperfusion. Whether coronary patency is or is not achieved will probably determine the size of infarction.[20] In contrast, Castaigne et al[21] found that ejection fractions were not significantly higher in patients who received APSAC at home, with a gain of approximately 60 minutes compared with patients who received APSAC after admission. Disparity of time of reperfusion in the 2 treatment groups of our study population, as indicated by mean time to creatine kinase peak, may be of minor importance for infarct size as assessed by scintigraphic parameters and global ejection fraction. Further studies will have to clarify this point.

Tl-201/Tc-99m pyrophosphate uptake pattern: The second question of the present study was to elucidate the interrelation between Tl-201/Tc-99m PYP ac-

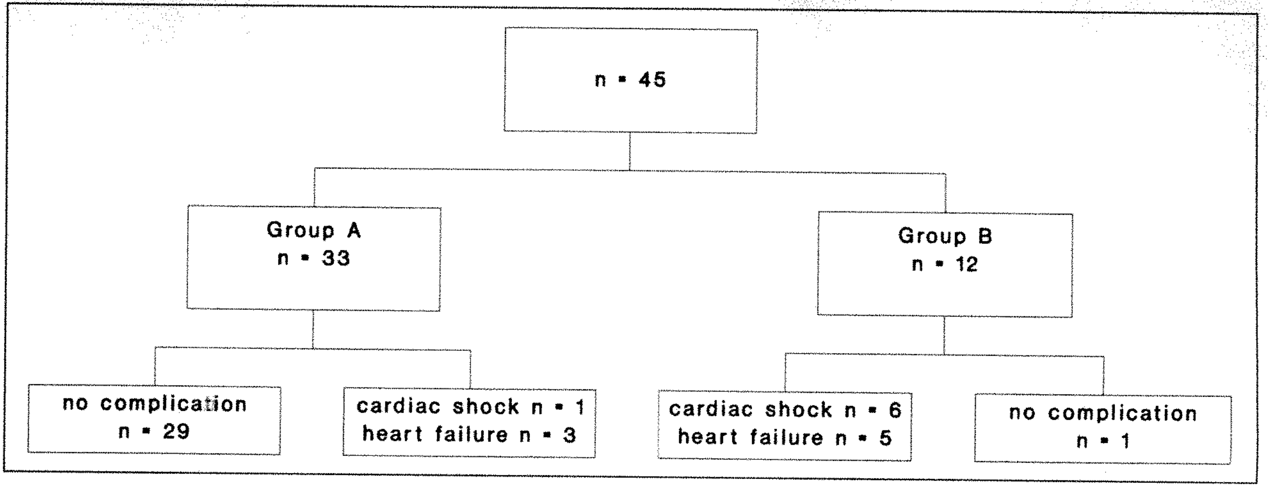

FIGURE 2. Diagram of correlation between scintigraphic patterns and clinical course in all patients independent of therapy.

cumulation pattern and clinical findings, which has not been described until now. In this study, creatine kinase maximal peak was not different in both group A with a homogeneous pattern and group B with an inhomogeneous pattern. However, global left ventricular ejection fraction was higher and scintigraphic infarct size was lower in group A. These results strongly suggest that an inhomogeneous pattern is associated with a larger AMI size than is usually seen in patients with a homogeneous accumulation pattern. Furthermore, the significantly shorter time to creatine kinase peak in group A suggests a relation between scintigraphic pattern and time to coronary perfusion. The inhomogeneous pattern was generally associated with increased activity accumulation of Tc-99m PYP in the border infarct periphery, as indicated by Tl-201 defect and decreased Tc-99m PYP uptake at the center. Prior studies described partial flow dependency of Tc-99m PYP uptake within necrosis.[22,23] Tc-99m PYP accumulation was found to achieve a maximum in the range between 31 and 50% of control flow.[24,25] Only moderate or extremely reduced Tc-99m PYP uptake was seen at low flow. Thus, it is likely that residual perfusion is required for homogeneous Tc-99m PYP uptake to the infarct area. Actually, 97% of the patients in group A had a patent infarct-related vessel, whereas 36% of the patients in group B showed an occlusion. However, the fact that coronary angiography was performed 2 to 3 weeks after AMI makes this finding less convincing than it might possibly have been otherwise. Nevertheless, the hypothesis of Rude et al[26] concerning the development of the doughnut pattern as found with planar imaging technique is supported. From our results drawn by tomographic imaging, it is likely that an inhomogeneous accumulation corresponds to the doughnut pattern and is due to occlusion of the infarct-related vessel, as suggested by Rude et al,[26] or due to lack of capillary reperfusion (no reflow).[27] In contrast to planar imaging,[26] the tomographic technique enables identification of a inhomogeneous pattern even of the inferior wall.

Clinical course: Patients with an inhomogeneous accumulation pattern (group B) had a higher risk of severe heart failure or cardiogenic shock. Other complications such as angina pectoris, arrhythmia, reinfarction or atrioventricular block were not related to a particular accumulation pattern. These findings were in agreement with the data reported for the doughnut pattern in anterior infarction by Rude and co-workers.[26] However, the results of the present study were more obvious. A primary reason for the higher morbidity in group B patients was that they may have had progressive infarct expansion. In animals, even late reperfusion resulted in much less infarct expansion compared with permanent occlusion.[28] Finally, infarct expansion, persistently occluded infarct-related coronary arteries and large infarcts appear to be risk factors for progressive left ventricular dilatation.[29]

In contrast, Botvinick et al[30] found a larger extent of Tc-99m PYP accumulation and Tl-201 defect in symptomatic patients and in decreased patients than in asymptomatic patients. However, their data enabled identification of only 5 of 8 symptomatic patients. The Tl-201/Tc-99m PYP pattern described in this present study provides more accurate prognosis regarding an adverse clinical course than conventional scintigraphic parameters.

REFERENCES

1. Maddahi J, Ganz W, Ninomiya K, Hashid J, Fishbein MC, Mondkar A, Buchbinder N, Marcus H, Geft I, Dhah PK, Rozanski A, Swan HJC, Berman DS. Myocardial salvage by intracoronary thrombolysis in evolving acute myocardial infarction: evaluation using intracoronary injection of thallium-201. Am Heart J 1981;102:664–674.

2. Okada RD, Boucher CA. Differentiation of viable and nonvia- able myocardium after acute myocardial reperfusion using serial thallium-201 imaging. Am Heart J 1987;113:241–250.

3. Schofer J, Strizke P, Montz R, Bleifeld W, Mathey DG. Assessment of myocardial necrosis immediately after intracorry thrombolysis by intracoronary technetium-99m pyrophosphate. Eur Heart J 1985;6:33–42.

4. Wheelan K, Wolffe C, Corbett J, Rude RE, Winniford M, Parkey RW, Buja LM, Willerson JT. Early positive technetium-99m stannous pyrophosphate images as a marker of reperfusion after thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1985;56:252–256.

5. Berger HJ, Gottschalk A, Zaret BL. Dual radionuclide study of acute myocardial infarction: comparison of thallium-201 and Tc-99m stannous pyrophosphate imaging in man. Ann Intern Med 1978;88:145–154.

6. Schofer J, Mathey DG, Montz R, Bleifeld W, Strizke P. Use of dual intracoronary scintigraphy with thallium-201 and technetium-99m pyrophosphate to predict improvement in left ventricular wall motion immediately after intracoronary thrombolysis in acute myocardial infarction. J Am Coll Cardiol 1983;2:737–744.

7. Hashimoto T, Kambara H, Tetsuro F, Tamaki S, Takatsu Y, Hattori R, Tohunaga S, Kawai C, Uozu K. Significance of technetium-99m/thallium-201 overlap on simultaneous dual emission computed tomography in acute myocardial infarction. Am J Cardiol 1988;61:1181–1186.

8. Johnson LL, Seldin DW, Keller AM, Wall RM, Bhatia K, Binghamm III CO, Tresgallo ME. Dual isotope thallium and indium antimyosin SPECT imaging to identify acute infarct patients at further ischemic risk. Circulation 1990;81:37–45.

9. Krause T, Zeiher A, Kasper W, Schümichen C, Moser E. Relation of Tc-99m pyrophosphate accumulation to time interval after onset of acute myocardial infarction as assessed by a tomographic acquisition technique. Am J Cardiol 1991;68:1575–1579.

10. Meinertz Th, Kasper W, Schumacher M, Just H. The German multicenter trial of anisoylated plasminogen streptokinase activator complex versus heparin for acute myocardial infarction. Am J Cardiol 1988;62:347–351.

11. Krause Th, Schümichen C, Fischer R, Strauss E, Hoffmann G. Simultaneous 201Tl/99m Tc-seven-pinhole tomography in acute myocardial infarction. Nucl Med 1986;25:99–105.

12. Buja LM, Parkey RW, Stokely EM, Bonte FJ, Willerson JT. Pathophysiology of technetium-99m stannous pyrophosphate and thallium-201 scintigraphy of acute anterior myocardial infarcts in dogs. J Clin Invest 1976;57:1508–1522.

13. Vogel RA, Kirch D, LeFree M, Steele P. A new method of multiplanar emission tomography using a seven pinhole collimator and an Anger scintillation camera. J Nucl Med 1978;19:648–654.

14. Stirner H, Büll U, Kleinhans E. Three-dimensional ROI-based quantitation of stress/rest 201Tl myocardial SPECT: presentation of method. J Nucl Med 1986;25:128–133.

15. Krause T, Joseph A, Kutzner C, Kasper W, Schümichen C, Just H, Moser E. Acute myocardial infarction delineated by noninvasive thallium 201/technetium-99m pyrophosphate tomography. Nucl Med Commun 1990;11:617–629.

16. Schröder R, Biamino G, Von Leitner E-R, Lindner T, Brüggemann T, Heitz J, Vöhringer H-F, Wegschneider K. Intravenous short-term infusion of streptokinase in acute myocardial infarction. Circulation 1983;67:635–648.

17. Kasper W, Meinertz Th, Wollschläger H, Bonzel T, Chen C, Hofmann T, Zeiher A, Drexler H, Just H. Early clinical evaluation of the intravenous treatment of acute myocardial infarction with anisoylated plasminogen streptokinase activator complex. Drugs 1987;33(suppl 3):112–116.

18. AIMS trial study group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet 1988;1:545–549.

19. Bassand JP, Bernard Y, Lusson JR, Machecourt J, Cassagnes J, Borel E. Effects on infarct size and left ventricular function of early intravenous injection of anistreplase in acute myocardial infarction. The APSIM study investigators. Clin Cardiol 1990(suppl 5):V39–V44.

20. Maublant JC, Peycelon P, Cardot JC, Verdent J, Fagret D, Comet M. Value of myocardial defect size measured by thallium-201 SPECT: results of a multicenter trial comparing heparin and a new fibrinolytic agent. J Nucl Med 1988;29:1486–1491.

21. Castaigne AD, Herve C, Duval-Moulin AM, Gaillard M, Dubois-Rande JL, Boesch C, Wolf M, Lellouche D, Jan F, Vernant P, Huguenard P. Prehospital use of APSAC: results of a placebo-controlled study: Am J Cardiol 1989;64:30A–33A.

22. Long R, Symes J, Allard J, Burdon T, Lisbona T, Huttner I, Sniderman A. Differentiation between reperfusion and occlusion myocardial necrosis with technetium-99m pyrophosphate scans. Am J Cardiol 1980;46:413–418.

23. Parkey RW, Kulkarni PV, Lewis SE, Datz FL, Dehmer GJ, Gutekunst DP, Buja LM, Bonte FJ, Willerson JT. Effect of coronary blood flow and site of injection on Tc-99m PPi detection of early canine myocardial infarcts. J Nucl Med 1981;22:133–137.

24. Sochor H, Schwaiger M, Schelbert HR, Ellison D, Hansen H, Seling C, Grover M, Parodi SC, Phelps ME. Tissue characterization of reperfused myocardium: conventional markers versus metabolic indices. In: Hoefer R, Bergmann H, eds. Radioaktive Isotope in Klinik und Forschung. Gasteiner Internat. Symposium. Wien: H. Egerman, 1986;17:271–277.

25. Zaret BL, DiCola FC, Donabedian RK, Puri S, Wolfson S, Freedman DG, Cohen LS. Relationship between myocardial uptake of potassium-43, Tc-99m stannous pyrophosphate, regional myocardial blood flow and creatine phosphokinase depletion. Circulation 1976;53:422–428.

26. Rude RT, Parkey RW, Bonte FJ, Lewis SE, Twieg D, Buja LM, Willerson JT. Clinical implications of the technetium-99m stannous pyrophosphate myocardial scintigraphic "doughnut" pattern in patients with acute myocardial infarcts. Circulation 1979;59:721–730.

27. Schofer J, Montz R, Mathey DG. Scintigraphic evidence of the "no reflow" phenomenon in human beings after coronary thrombolysis. J Am Coll Cardiol 1985;5:593–598.

28. Hochmann JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. Circulation 1987;75:299–306.

29. Lamas GA, Pfeffer MA, Braunwald E. Patency of the infarct-related coronary artery and ventricular geometry. Am J Cardiol 1991;68:41D–51D.

30. Botvinick EH, Perez-Gonzalez JF, Dunn R, Ports T, Chatterjee K, Parmley W. Late prognostic value of scintigraphic parameters of acute myocardial infarction size in complicated myocardial infarction without heart failure. Am J Cardiol 1983;51:1045–1051.

Blood Viscosity During Thrombolytic Therapy with Anistreplase in Acute Myocardial Infarction

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It has been postulated that a reduction in blood viscosity due to degradation of plasma fibrinogen may be of benefit to patients with acute myocardial infarction (AMI), who are treated with thrombolytic agents. The aims of this study were to investigate the time course of rheologic parameters, to identify the principal factors determining blood viscosity, and to find possible correlations between viscosity and cardiac function during thrombolytic therapy with anistreplase. Therefore, the viscosity of whole blood and plasma and the hematocrit were measured before and at 10 time points after thrombolysis in 10 patients with AMI. In addition, plasma fibrinogen and fibrin(ogen) degradation products were determined. Immediately after the start of thrombolysis, the viscosity of blood (both at high and low shear rate) and plasma decreased significantly and continued to do so for 24 hours. The mean hematocrit also decreased markedly, and even after correction for these hematocrit changes, the reduction in blood viscosity remained significant: it decreased to 72% of pretreatment (measured at low shear rate), whereas the high-shear viscosity decreased to 95% of baseline. The viscosity of plasma significantly decreased from 1.39 ± 0.13 mPa • s (mean ± SD) before thrombolysis to 1.22 ± 0.08 mPa • s after 2 hours. There was a rapid, nearly complete depletion in fibrinogen, followed by a striking rebound after the second day. The decrease in blood viscosity lasted for 2 days after anistreplase and was mainly accounted for by the reduction in hematocrit. The contribution of fibrinogen to blood viscosity appeared less prominent. Despite these rheologic changes, no improvement in cardiac output was noticed in the patients.

(Am J Cardiol 1993;71:14–18)

In the early phase after acute myocardial infarction (AMI), the rheologic conditions in coronary vessels may be rather unfavorable. Apart from the impaired flow in the microcirculation distal to the occlusive thrombus, the viscosity of blood is increased because of a high hematocrit[1] and an increase in plasma fibrinogen concentration.[1–4] This increase in viscosity may contribute considerably to the evolving myocardial necrosis, since oxygen supply to the myocardial tissue inversely depends on blood viscosity.[2] By restoring patency, thrombolytic therapy improves the flow conditions in the coronary circulation. Additional improvement of blood rheology by lowering the increased viscosity may be advantageous in terms of oxygen supply and salvage of viable myocardial tissue. Because fibrinogen is a major determinant of blood viscosity, thrombolytic drugs that cause extensive fibrinogen breakdown could offer this additional benefit. In the past, streptokinase was shown to decrease plasma viscosity[4–6] and more recent data confirm the higher reduction in plasma viscosity obtained with the less fibrin-selective thrombolytic agents.[7–10] However, the alleged clinical benefit of reduced viscosity has not been proven. The present study documents the time course of blood and plasma viscosity in patients with AMI treated with anistreplase. Furthermore, we sought to identify the major factors influencing blood viscosity during thrombolysis and to correlate changes in viscosity with cardiac output after thrombolytic therapy.

METHODS

Patients: Ten patients, 9 men and 1 woman (mean age 60 years [range 50 to 68]) presented with typical signs of AMI and were included in the study within 4 hours from onset of chest pain. Nine patients had an inferior AMI and 1 had an anterior infarction. None had experienced a previous AMI. The usual criteria for inclusion and exclusion were applied, except that the use of aspirin or other antiplatelet drugs was reason for exclusion, because these patients simultaneously participated in a study on the influence of thrombolysis on platelet function. On the average 2.4 hours (range 1.2 to 4.2 hours) after beginning of chest pain, anistreplase (Anisoylated Plasminogen Streptokinase Activator Complex, Eminase® 30 U) was administered by intravenous injection over 2 to 5 minutes. Heparin was begun 3 hours later by continuous intravenous infusion; its dose was adjusted according to the activated partial thromboplastin time. At 60, 75 and 90 minutes after

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starting the thrombolysis, coronary angiography was performed for assessing coronary patency and at 90 minutes cardiac output was measured using the thermodilution technique. Assessment of patency and cardiac output were repeated after 48 hours. Before and after anistreplase, blood was collected for determining the rheologic and hemostatic parameters as specified later. Blood sampling was complete in 4 patients, 1 sample was missing in each of 4 other patients and 2 patients had 2 missing samples; at all time points ≥ 8 observations were available. The study protocol had been approved by our hospital's ethical committee and patients gave their informed consent before inclusion.

Methods: Blood for viscosity determinations was collected into tripotassium ethylenediaminetetraacetic acid (final concentration 1 mg/ml), supplemented with aprotinin (final concentration 250 KIU/ml) in order to prevent in vitro fibrinogenolysis. Viscosity was measured within 1 hour from blood sampling using a rotational viscosimeter (LS-30; Contraves AG, Zürich, Switzerland). Native blood viscosity, i.e., at the actual hematocrit, was determined at 2 different shear rates — 128.5 s^{-1} (high shear) and 1.3 s^{-1} (low shear), according to the International Committee for Standardization in Haematology recommendations.[11] Standardized blood viscosity at either shear rate was corrected to a hematocrit of 0.45 as described by Matrai et al.[12]

For determining coagulation parameters, blood was drawn into citrate, which was supplemented with aprotinin (final concentrations 0.01 M and 250 KIU/ml, respectively) and centrifuged for 15 minutes at 3,000 g at 4°C; the plasma was snap-frozen in liquid nitrogen and stored at -70°C until analysis. Standard methods[13] and commercially obtained reagents were used. Fibrinogen was determined using the Clauss clotting rate method, and fibrin and fibrinogen degradation products by specific enzyme immunoassays based on monoclonal antibodies (Fibrinostika; Organon, Boxtel, the Netherlands).

Statistical evaluation of changes over time points was done using a univariate repeated measurements analysis of variance. In case of significance this was followed by a paired *t* test between data at baseline and the other time points. Multiple regression analysis was performed using the pooled data across all time points. A p value < 0.05 was considered significant.

RESULTS

Clinical: Coronary patency was observed after 90 minutes in 9 of 9 patients (1 patient had coronary angioplasty after 60 minutes), and after 48 hours no reocclusion was seen. These results are not essentially different from what is usual for anistreplase therapy.

Rheology: The pretreatment blood viscosity was within the normal range in all patients, both at low and at high shear rates. After administration of the thrombolytic drug there was a rapid decrease in native blood viscosity, which reached its lowest value 24 hours later. At that time, the native blood viscosity was 77% of pretreatment value ($p < 0.001$) at high shear rate and 49% of baseline value ($p < 0.001$) at low shear rate (Figure 1). Hereafter, the mean blood viscosity gradually increased but it was still lower than the initial value before discharge, 7 to 9 days after thrombolysis. The mean hematocrit decreased steadily during the entire observation period (Figure 1).

When the blood viscosity was standardized to a hematocrit of 0.45, a different picture was seen. The low-shear blood viscosity was minimal after 12 hours (72% of baseline; $p < 0.02$) and the high-shear viscosity decreased to 95% of pretreatment values ($p < 0.05$), also at 12 hours (Figure 1). Both parameters returned to their baseline values after the second day and had increased significantly above pretreatment values before discharge.

The viscosity of plasma was initially normal in all patients but 1, in whom it was elevated; mean ± SD 1.39 ± 0.13 mPa • s. It decreased sharply in all patients immediately after administration of anistreplase (Figure 2). After 2 hours the mean plasma viscosity was 1.22 ± 0.08 mPa • s, or 88% of baseline; this difference was significant ($p < 0.01$). From 90 minutes up to 24 hours the mean plasma viscosity remained more or less stable and then started to increase. Before discharge it had increased to 104% of the baseline value: 1.45 ± 0.14 mPa • s ($p = 0.033$; Figure 2).

Fibrinogen: All patients had normal fibrinogen before treatment, ranging from 2.9 to 4.0 g/liter (mean 3.33 ± 0.45). After only 30 minutes, a considerable decrease in fibrinogen was apparent amounting to 13% of pretreatment value ($p < 0.001$). The nadir, at 4% of baseline values was observed after 2 hours and fibrinogen remained very low until 12 hours (Figure 3). Then, a rapid increase became manifest, crossing the pretreatment value after the second day. This fibrinogen rebound was still present before discharge, when the mean concentration was 36% above the pretreatment value (4.53 ± 0.52 g/liter; $p < 0.002$).

Fibrin(ogen) degradation products and coagulation factors: The decrease in fibrinogen was accompanied by a rapid, marked increase in the concentration of

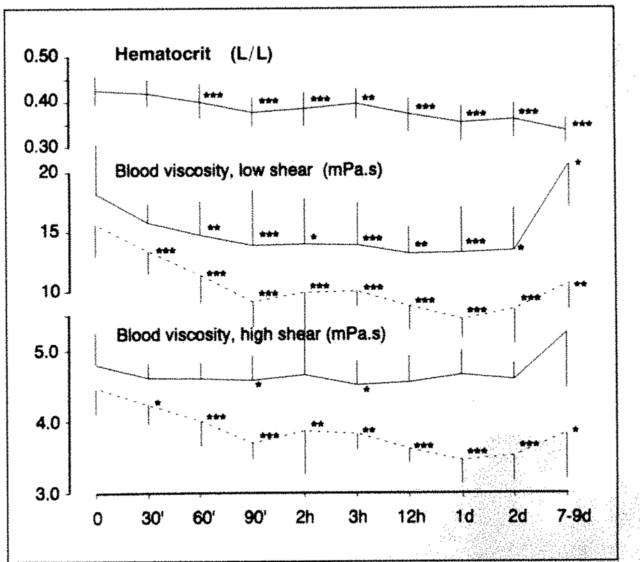

FIGURE 1. Course of rheologic parameters during thrombolytic therapy. In the *middle* and *lower frames, dotted lines* represent the native blood viscosity and the *solid lines* the standardized viscosity, corrected to a hematocrit of 0.45. *Vertical lines,* mean ± SD. Difference from pretreatment values: *p <0.05; **p <0.01; and ***p <0.001.

fibrinogen degradation products. It reached its maximum after 60 minutes (mean 429 mg/liter, range 80 to 820) and then slowly decreased. At days 7 to 9, the concentration was still above the normal range in almost all patients (Figure 3).

The degradation products of cross-linked fibrin also significantly increased, but with a profile different from that of the fibrinogen degradation products. The highest value was observed after 12 hours (mean 11.3 ± 5.3 mg/liter) and the rate of increase was only moderate. Before discharge, it was still elevated in all patients in whom it was measured.

Other coagulation proteins exhibited the expected pattern. Plasminogen activity significantly decreased (to about 12% of pretreatment at 3 hours), α_2-antiplasmin activity became very rapidly entirely depleted (mean <0.10 U/ml after 30 minutes) and the euglobulin clot lysis time was extremely shortened (<15 minutes) in all patients, 60 minutes after administration of anistreplase ($p < 0.001$); the profiles were closely comparable to that of fibrinogen. These parameters had essentially returned to baseline levels by day 2 (data not shown).

Cardiac function: Cardiac output was 6.5 ± 2.0 liters/min at 90 minutes and it decreased to 4.9 ± 1.2 liters/min by 48 hours after start of thrombolysis. Mean left ventricular ejection fraction was 75 ± 10% (range 63 to 87) at 90 minutes and 66 ± 16% (range 36 to 84) after 48 hours.

Regression models: We analyzed the pooled data of all patients in order to find the major determinants of viscosity during thrombolysis and their relative importance. The native blood viscosity (low shear) significantly correlated with the hematocrit ($r = 0.681$; $p < 0.0001$) and with fibrinogen ($r = 0.249$; $p < 0.02$), but not with the concentration of fibrinogen degradation products ($r = 0.01$; p = not significant [NS]). The total variance in low shear blood viscosity was explained for 50% by the variance in the hematocrit and for another 13% by that in fibrinogen; the addition of fibrinogen degradation products did not further improve the regression model.

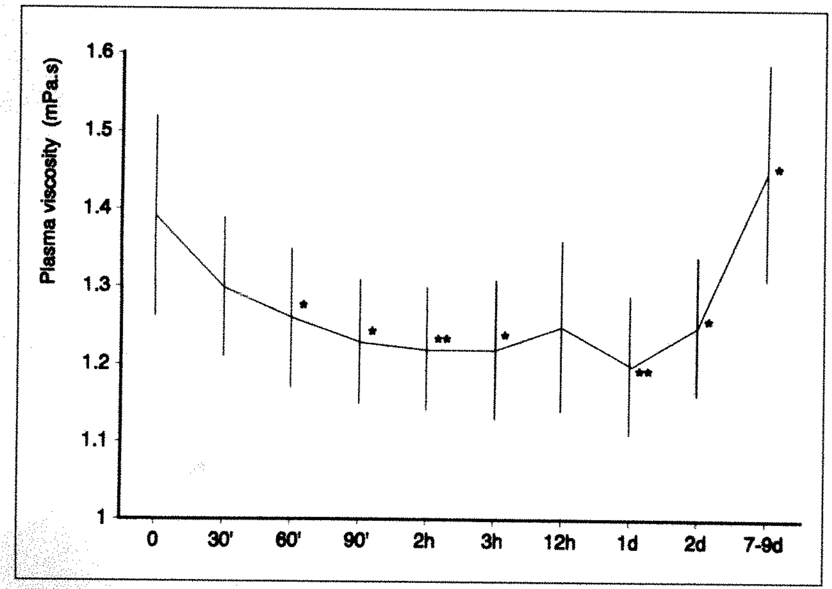

FIGURE 2. Plasma viscosity as a function of time after thrombolysis (mean ± SD). Difference from baseline: *p <0.05 and **p <0.01.

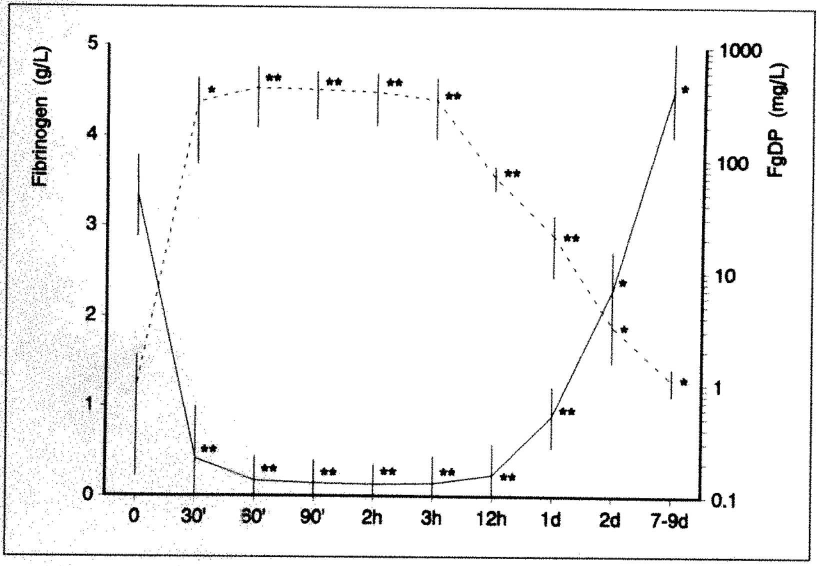

FIGURE 3. Fibrinogen *(solid line)* and fibrinogen degradation products (FgDP; *dotted line*) during the study period (mean ± SD). Difference compared with pretreatment values: *p <0.01 and **p <0.001.

Similarly, the correlation between high shear blood viscosity and the hematocrit was significant ($r = 0.739$; $p<0.0001$). However, the high shear blood viscosity was only weakly correlated with fibrinogen ($r = 0.166$; $p = 0.112$) and not at all with fibrinogen degradation products ($r = 0.08$; p = NS). The hematocrit was the main determinant of blood viscosity at high shear rate, explaining 57% of its variance, followed by fibrinogen, which added 8% to the variance.

The most important parameter determining the plasma viscosity under the circumstances studied was fibrinogen. It contributed 28% to the variance in plasma viscosity and was significantly correlated with it ($r = 0.537$; $p <0.0001$). Again, the concentration of fibrinogen degradation products conveyed no explanation to the variance in plasma viscosity.

There was no correlation of cardiac output with either blood viscosity ($r = -0.154$; p = NS), plasma viscosity ($r = -0.216$; p = NS) or fibrinogen ($r = -0.508$; p = NS).

DISCUSSION

Thrombolytic therapy can be regarded as the standard treatment of patients with AMI. Among the numerous studies on various aspects of thrombolytic therapy, little attention has been given to its rheologic effects. It has always been postulated that reducing the viscosity of blood by extensive degradation of fibrinogen by means of thrombolytic drugs might be beneficial to the patient,[4–6] but this hypothesis has never been substantiated.

To adequately appreciate the relevance of blood rheology for AMI and its thrombolytic treatment, some basic concepts of viscosity should be addressed.[14] The movement of blood in a vessel is not homogenous: the flow pattern is best represented by an infinite number of concentrical fluid layers, each of which moves with a discrete velocity. The velocity of the central layer is higher than that of more eccentric layers; so, a faster layer slides over an adjacent, more slowly moving layer of fluid. This process is called shearing. The velocity gradient over the fluid, i.e., the difference in velocity in relation to the distance between layers, is the shear rate. The force necessary to make a layer sliding over an adjacent one at a given shear rate is only dependent on material property of the fluid, called its dynamic viscosity coefficient or its viscosity. In ideal, so-called Newtonian, fluids the viscosity is independent of the flow conditions and thus independent of the shear rate. However, owing to its high content of red cells, blood is a non-Newtonian fluid, and hence its viscosity is dependent on the prevailing shear rate. At high shear rates, the contribution of red cells to blood viscosity is relatively low, because they have only a slight tendency to form aggregates. However, under low shear conditions the red cells are predisposed to aggregate and this causes a dramatic increase in viscosity. Thus, it is not possible to define the viscosity of blood, but only to measure it at a given shear rate or range of different shear rates. In vivo, high shear rates (≥ 200 s^{-1}) prevail in arteries and large veins, whereas low shear rates (20 to 50 s^{-1}) are encountered in small venules.[1] In AMI, the shear rate in coronary vessels distal to the occlusive thrombus may be extremely low, ≤ 20 s^{-1}.[1] By convention, blood viscosity is reported at a low and a high shear rate.[14] Accordingly, we have chosen to measure blood viscosity at 1.3 and 128.5 s^{-1}, respectively. Because the hematocrit is one of the major determinants of blood viscosity, we calculated the standardized viscosity in addition to the native viscosity; the standardized viscosity is corrected for and therefore no longer dependent on the actual hematocrit.[12]

Our results confirm that thrombolytic therapy with a drug that causes a profound systemic lytic state significantly reduces the viscosity of blood and plasma. The decrease in standardized blood viscosity found here — 28% (low shear) and 5% (high shear) — is comparable to the values found by Arntz et al,[8] who described a 16 and 9% decrease, respectively, after the same dose of anistreplase, but at slightly different shear rates, namely 5.75 and 115 s^{-1}. The 12% reduction in plasma viscosity found by us (Figure 2) is very close to their finding of a 15% decrease.[8] These values are equivalent to the reduction in plasma viscosity by 7 to 19%, described after high-dose streptokinase,[4–6,8,10] and are 2 to 3 times higher than those after treatment with tissue-plasminogen activator.[10] This is not surprising when considering the limited systemic fibrinogenolysis by tissue-plasminogen activator compared with streptokinase and anistreplase. The latter caused an extensive depletion of plasma fibrinogen in the present study (Figure 3).

The high correlation between plasma viscosity and fibrinogen corroborates the importance of this protein as a determinant of the viscous properties of plasma.[14] However, this correlation was challenged by 2 factors: We performed the regression analysis on pooled data (which ignores the interdependence of observations from a single patient and could lead to overestimation of a correlation), whereas the sometimes undetectable fibrinogen values prohibited estimating the exact contribution of fibrinogen to the variance in viscosity (a potential source of underestimation).

Furthermore, the contribution of fibrinogen degradation products to plasma and blood viscosity was not significant, even at the very high concentrations prevailing during the early phase after anistreplase. This is distinct from the findings by Rampling et al,[15] who in an in vitro study on the rheologic effects of fibrinogen and its degradation products, found that all degradation products caused measurable effects on viscosity, although significantly less than intact fibrinogen. Even the small, late fragments still had viscometric effects.[15] However, in their experiments aqueous solutions were used to create red cell suspensions, whereas we used plasma. It is conceivable that effects of fibrinogen degradation products could not be distinguished from the effects of other plasma proteins on the plasma viscosity. Although fibrinogen fragments may have certain effects on the viscosity of plasma and blood, our data suggest that these effects are probably not large enough to make a relevant contribution to in vivo blood rheology.

The discordant changes in native and standardized blood viscosity indicate that the decrease in hematocrit observed during the treatment plays an important role in the improvement of blood rheology. This was further accentuated by the regression analysis, which showed that the contribution of the hematocrit to blood viscosity was 4 to 7 times greater than that of fibrinogen (again, the influence of fibrinogen has possibly been underrated, as previously indicated). Because a thrombolytic agent itself is unlikely to cause a decrease in hematocrit, the hemodilution noticed must be explained by other factors such as fluid balance, medication and infusion policy. From earlier studies it is known that a decrease in hematocrit is frequently seen after AMI, even without thrombolytic treatment.[1,2,6] Moreover, it has previously been shown that contrast agents used in coronary angiography caused hemodilution because of their osmotic effect.[16] In the present study, repeated angiographies were performed, and therefore the hemodilution induced in the early phase may have been even larger than that during standard thrombolytic treatment.

Extrapolating our results may mean that the improvement of hemorrheology during thrombolytic treatment is only partially the consequence of the fibrin selectivity of the thrombolytic agent administered. Some support for this inference, although partial and indirect, is provided by a recent study of Bassand et al.[17] They found no significant differences in left ventricular ejection fraction, regional wall motion, infarct size and in-hospital mortality between anistreplase and tissue-plasminogen activator, despite large differences in fibrinogen breakdown. Had the degree of systemic fibrinogenolysis (and thus blood viscosity) had important effects on these cardiac parameters, perceptible differences might have been found in this trial using 2 drugs with dissimilar effects on fibrinogen. In the present study, no correlation was found between the reduction in viscosity and cardiac output, but the number of observations may have been too low for detecting such a relation.

Acknowledgment: We are most grateful to Mia Vijgen and Petra Custers for their expert technical assistance, to Robin Fears, PhD, for his contribution to initiating this study, and to Peter Ochlich, PhD, for lending the viscosimeter. The statistical analyses were kindly performed by Jaap Couvée and Suzanne Loriaux.

REFERENCES

1. Jan KM, Chien S, Bigger JT Jr. Observations on blood viscosity changes after acute myocardial infarction. *Circulation* 1975;51:1079–1084.

2.Gordon RJ, Snyder GK, Tritel H, Taylor WJ. Potential significance of plasma viscosity and hematocrit variations in myocardial ischemia. *Am Heart J* 1974;87:175–182.

3. Chmiel H, Effert S, Mathey D. Rheologische Veränderungen des Blutes beim akuten Herzinfarkt und dessen Risikofaktoren. *Dtsch Med Wochenschr* 1973;98:1641–1646.

4. Theiss W, Volger E, Wirtzfeld A, Keisel I, Blömer H. Gerinnungsbefunde und rheologische Messungen bei Streptokinasebehandlung des akuten Myokardinfarktes. *Klin Wochenschr* 1980;58:607–615.

5. Schmid-Schönbein H, Rieger H, Hess H. Quantitative Erfassung der Effekte fibrinolytischer Therapie auf das Fliessverhalten des Blutes. *Klin Wochenschr* 1977;55:111–119.

6. Moriarty AJ, Hughes R, Nelson SD, Balnave K. Streptokinase and reduced plasma viscosity: a second benefit. *Eur J Haematol* 1988;41:25–36.

7. Douglas JT, Gemmill JD, Hogg KJ, Rae AP, Dunn FG, McGregor IR, Hillis WS, Lowe GDO. Haemostatic and haemorheological changes and coronary reperfusion following bolus injection of rt-PA in acute myocardial infarction (abstr). *Fibrinolysis* 1990;4(suppl 1):68.

8. Arntz HR, Roll G, Heitz J, Schäfer JH, Schröder R. Effects of different thrombolytic agents on blood rheology in acute myocardial infarction. *Clin Hemorheol* 1991;11:63–78.

9. Pindur G, Sen C, Wenzel E, Jung F, Özbek C, Schwerdt H, Schieffer H, Bette L, Miyashita C. Modern strategies for treatment of acute myocardial infarction: significance of haemostaseological and rheological findings. *Adv Exp Med Biol* 1990;281:389–394.

10. Jan KM, Powers E, Reinhart W, Berke A, Nichols A, Watson R, Reison D, Schwartz A, Chien S. Altered rheological properties of blood following administration of tissue plasminogen activator and streptokinase in patients with acute myocardial infarction. *Adv Exp Med Biol* 1990;281:409–417.

11. International Committee for Standardization in Haematology (Expert Panel on Blood Rheology). Guidelines for measurement of blood viscosity and erythrocyte deformability. *Clin Hemorheol* 1986;6:439–453.

12. Matrai A, Whittington RB, Ernst E. A simple method of estimating whole blood viscosity at standardized hematocrit. *Clin Hemorheol* 1987;7:261–265.

13. Jespersen J, Bertina RM, Haverkate F. ECAT Assay Procedures. A Manual of Laboratory Techniques. Dordrecht: Kluwer Academic Publishers, 1992.

14. Lowe GDO. Blood rheology in vitro and in vivo. *Bailliere's Clin Haematol* 1987;1:597–636.

15. Rampling MW, Whittingstall P, Linderkamp O. The effects of fibrinogen and its plasmin degradation products on the rheology of erythrocyte suspensions. *Clin Hemorheol* 1984;4:533–543.

16. Hoffmann JJML, Bonnier JJRM, Bartholomeus I. Hemorheological effects of a nonionic contrast medium: an ex vivo study. *Clin Hemorheol* 1992;12:217–221.

17. Bassand J-P, Cassagnes J, Machecourt J, Lusson J-R, Anguenot T, Wolf J-E, Maublant J, Bertrand B, Schiele F. Comparative effects of APSAC and rt-PA on infarct size and left ventricular function in acute myocardial infarction. *Circulation* 1991;84:1107–1117.

Effects of Late (1 to 30 Days) Reperfusion After Acute Myocardial Infarction on the Signal-Averaged Electrocardiogram

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Early reperfusion (4 to 6 hours) after acute myocardial infarction reduces mortality and reduces the incidence of late potentials on a signal-averaged electrocardiogram (SAECG). Recent reports suggest that reperfusion accomplished after >6 hours also may reduce mortality. The effect of such later reperfusion on the SAECG is not known. We hypothesized that reperfusion by angioplasty accomplished >24 hours after onset of infarction would reduce late potentials and improve the parameters on the SAECG. Forty-one patients with a totally occluded infarct-related artery 12 ± 8 days after infarction underwent attempted angioplasty. SAECG, echocardiography and thallium-201 imaging were performed before and 1 month after attempted angioplasty. Angioplasty resulted in successful reperfusion in 32 patients and was unsuccessful in 9. No change in the incidence of late potentials occurred after successful reperfusion (13 of 32 patients before and 13 of 32 patients 1 month later) or after unsuccessful reperfusion (6 of 9 patients before and 5 of 9 patients 1 month later). Among patients with successful reperfusion, no significant change occurred in the QRS duration or the terminal signal duration <40 μV. The terminal root-mean-square voltage in microvolts improved significantly at 1 month (31 ± 25 before to 38 ± 29 after, $p = 0.004$). Twenty-two of 32 patients with successful reperfusion had improved wall motion in the infarct zone at 1 month. Despite an improvement in function in these patients, no change in the incidence of late potentials occurred by 1 month. Among patients with successful reperfusion, those without late potentials at baseline had improved wall motion to a greater extent than those with late potentials (change in wall motion score, 1.5 ± 0.9 vs 0.6 ± 0.8, $p = 0.009$). It is concluded that late reperfusion after acute myocardial infarction has little effect on the SAECG, and a normal SAECG in patients with a totally occluded artery after infarction may signify the presence of viable myocardium.

(Am J Cardiol 1993;71:19–23)

Thrombolytic therapy administered within the first 4 to 6 hours of myocardial infarction decreases the incidence of late potentials on a signal-averaged electrocardiogram (SAECG).[1–4] This benefit was observed only in patients in whom thrombolysis successfully restored patency of the infarct-related artery[1,5] and may reflect a decreased probability for developing ventricular arrhythmias. It has been suggested that reperfusion >6 hours after myocardial infarction may also reduce mortality.[6–9] Furthermore, an open infarct-related artery after acute myocardial infarction, even in the absence of early reperfusion, has been associated with reduced mortality.[10,11] A possible benefit of late reperfusion and an open infarct-related artery may be a beneficial effect on the electrophysiologic properties of the infarcted myocardium, resulting in a decreased tendency for ventricular arrhythmias. Based on the relation between serious ventricular arrhythmias and abnormalities of the SAECG,[12–14] one might expect a benefit of late reperfusion on serious ventricular arrhythmias to be reflected in an improvement in the SAECG.[4] Accordingly, we hypothesized that patients who undergo successful late reperfusion, defined as >24 hours after acute myocardial infarction, will have less late potentials and improved parameters on the SAECG compared with those with a persistently occluded artery. In addition, because both late potentials and a failure to improve function despite successful reperfusion might indicate nonviable myocardium in the infarct zone, we hypothesized that patients with late potentials would have less improvement in regional wall motion in the infarct zone than patients without late potentials. To test these hypotheses we performed a study using coronary angioplasty >24 hours after the onset of acute infarction to achieve reperfusion in patients with a totally occluded infarct-related artery.

METHODS

The study protocol was approved by the Human Investigations Committee of the University of Virginia and all patients gave informed consent. Forty-one consecutive patients (mean age of 56 ± 9 years) were enrolled. Patients were included if they underwent angioplasty of

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TABLE I Patient Characteristics

No. of patients	41
Location of acute myocardial infarction	
Anterior	12 (29%)
Inferior	27 (66%)
Lateral	2 (5%)
Failed thrombolysis	13 (32%)
Prior myocardial infarction	9 (22%)
Ejection fraction	0.53 ± 0.12

a totally occluded infarct-related artery >24 hours and <33 days (mean 12 ± 8 days) after acute myocardial infarction. We excluded patients with a paced rhythm or bundle branch block. Only 1 patient was taking antiarrhythmic medication.

Study protocol: Before and 1 month after attempted angioplasty, 2-dimensional echocardiography, thallium-201 imaging and signal-averaged electrocardiography were performed.

Echocardiography: Two-dimensional echocardiography was performed using 4 standard views. Echocardiograms were interpreted by 2 observers unaware of the clinical data and the results of angioplasty. Interobserver variability in our laboratory is good and has been previously reported.[15] The infarct zone was identified as that region corresponding to the infarct-related artery showing abnormal wall motion; this zone was graded as showing normal function, mild hypokinesia, severe hypokinesia, akinesia or dyskinesia, and graded 1 through 5, respectively. Studies obtained before and 1 month after angioplasty were compared and improvement in regional function was defined as improvement of wall motion in the infarct zone by at least 1 grade.

Thallium-201 imaging: Thallium-201 imaging was obtained before angioplasty and at 1 month after attempted angioplasty. For both studies, planar images were obtained immediately and 2 hours after the injection of 2.0 mCi of thallium-201 in the anterior, 45° and 70° left anterior oblique projections using a computer-assisted approach described previously.[16] An 11-segment model was constructed from the 3 views and activity in each segment was expressed as percentage of activity in the 9 9 pixel region with maximal activity in that view. The infarct segments were identified as those demonstrating hypoperfusion in the infarct vessel territory on the initial images. The mean thallium-201 activity within the infarct zone was calculated by averaging activity within the infarct bed from all views in the delayed images. Delayed images before and 1 month after angioplasty were compared for changes in thallium-201 activity within the infarct bed. Increase in activity by ≥5% was considered to represent improvement in thallium-201 uptake.

Signal-averaged electrocardiography: SAECGs were obtained using either the LP-3000 Late Potential Detector (Fidelity Medical Inc., Florham Park, New Jersey) or the Predictor Signal-Averaging Electrocardiogram System version 5.0 (Corazonix Corporation, Oklahoma City, Oklahoma). An orthogonal X, Y, Z lead system was used and signals from these leads were combined into a vector magnitude = $(x2 + y2 + z2)^{1/2}$. Using a time-domain mode with 40 Hz bidirectional filtering and a computer algorithm, the root-mean-square voltage of the terminal 40 ms of the filtered QRS, the duration of the filtered QRS and the terminal signal duration <40 uV were determined by an automated technique. Enough QRS complexes were obtained (mean 426 ± 417 beats) to achieve a noise level of <0.5 μV. A late potential was defined as present if the SAECG met 2 of 3 of the following criteria: filtered QRS duration >120 ms, terminal root-mean-square voltage <20 uV, or terminal signal duration <40 μV >38 ms.

Angioplasty: Angioplasty of the totally occluded infarct-related artery was attempted in all 41 patients. A patient was considered to have undergone successful reperfusion if the angioplasty was initially successful, resulting in a <30% residual stenosis with restoration of anterograde flow, and if there was no clinical evidence of reclosure (such as return of angina or reinfarction) before 1-month follow-up. All patients with clinically suspected reclosure or restenosis underwent coronary angiography. A patient was considered to have unsuccessful reperfusion if the total occlusion was not successfully crossed and dilated or, if initially successful, subsequent reclosure was documented by coronary angiography before 1-month follow-up.

Statistical analysis: All data were expressed as mean ± 1 SD. Data before and 1-month after angioplasty were compared using paired Student's *t* test or a 2-tailed Fisher's exact test when appropriate. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics: The clinical characteristics of the 41 patients are listed in Table I. Approximately one-third of the infarctions were anterior and two-thirds inferior. Thrombolytic therapy had been administered in 32%. However, all had an occluded infarct-related artery at the time of diagnostic catheterization. The remaining patients either had contraindications to lytic therapy or presented too late for lytic therapy based on current criteria. Mean global ejection fraction was 53% and only 22% had an old myocardial infarction. Reperfusion was considered successful in 32 patients (78%) and was unsuccessful in 9 (22%). Of these latter 9 patients, 2 had angiographically confirmed reclosure after an initially successful procedure while in 7, the initial angioplasty was not successful. Clinical characteristics were similar for those with and without successful reperfusion.

Signal-averaged electrocardiogram: Figure 1 depicts the percentage of patients with late potentials at baseline and at 1-month follow-up. Among patients with successful reperfusion, 13 of 32 (41%) at baseline and 13 of 32 (41%) at follow-up had late potentials. Among the 9 patients with a persistently closed infarct-related artery, 6 (67%) had late potentials at baseline, whereas 5 (56%) had them 1-month later. In addition to the lack of effect on the overall incidence of late potentials in the 2 groups, late reperfusion did not significantly affect the SAECG in individual patients (Figure 2). Among patients with successful reperfusion, 3 had a change in the SAECG from abnormal to normal, 3 had a change from normal to abnormal, and in 26 there was no change (Figure 2A). In the 9 patients with unsuccessful reperfusion, 1 had a change from abnormal to normal and 8 had no change (Figure 2B).

The effect of late reperfusion on the individual SAECG parameters is shown in Figure 3. Among patients with successful reperfusion, the mean QRS duration and terminal signal duration <40 µV did not significantly change at 1 month (QRS, 101 ± 12 ms before to 100 ± 11 ms after; terminal signal duration <40 µV, 35 ± 13 ms before to 34 ± 11 ms after). The average root-mean-square voltage improved at 1 month in the group of patients with successful late reperfusion (31 ± 25 µV before to 38 ± 29 µV after; $p = 0.004$). Patients with unsuccessful late reperfusion had no significant change in any of the 3 measured parameters (QRS, 115 ± 19 ms before to 120 ± 26 ms after; root-mean-square voltage, 21 ± 22 µV before to 22 ± 16 µV after; terminal signal duration <40 µV, 53 ± 21 ms before to 50 ± 33 ms after).

Although there was no significant difference in the incidence of late potentials in patients with successful versus unsuccessful reperfusion, the mean QRS duration and the terminal signal duration <40 µV were more abnormal at baseline before angioplasty among patients with subsequent unsuccessful reperfusion than in those with successful reperfusion (115 ± 19 vs 101 ± 12 ms [$p = 0.01$] and 53 ± 21 vs 35 ± 13 ms [$p = 0.004$], respectively).

Thallium-201: Thallium uptake in the infarction zone improved in 62% of patients with successful reperfusion and in only 13% of those with unsuccessful reperfusion. When patients whose baseline thallium showed a <20% defect are added to the group whose thallium uptake improved, the percentage of patients with either improved or essentially normal thallium scans at follow-up was 76% of those with successful reperfusion and remained at 13% of those with unsuccessful reperfusion. The prevalence of late potentials in patients whose thallium improved was the same at baseline and at 1 month (44 vs 50%, p = NS). In addition, in the subgroup of patients with successful reperfusion and an improvement in thallium uptake at 1 month, the individual SAECG parameters did not change from baseline to follow-up (QRS, 102 ± 16 ms before to 99 ± 13 ms after; root-mean-square voltage, 36 ± 31 µV before to 43 ± 35 µV after; terminal signal duration <40 µV, 36 ± 17 ms before to 35 ± 14 ms after, all p = NS).

Wall motion: For the entire group of patients with successful reperfusion, the wall motion score improved from 3.1 ± 1.0 to 1.9 ± 1.0 ($p = 0.0001$), whereas no improvement occurred in those with unsuccessful reperfusion (3.3 ± 0.7 to 3.6 ± 0.9, p = NS). Among patients with successful reperfusion, those with late potentials at baseline had less improvement in wall motion score than did those without late potentials (change in wall motion score 0.6 ± 0.8 vs 1.5 ± 0.9, $p = 0.009$). Among the 10 patients with successful reperfusion who had no improvement in wall motion, 7 (70%) had late potentials at baseline and 7 (70%) had late potentials at follow-up. Among 22 patients with successful reperfusion who had improved wall motion by at least 1 grade, 6 (27%) had late potentials at baseline and 6 (27%) had late potentials at follow-up. Thus, persistent myocardial

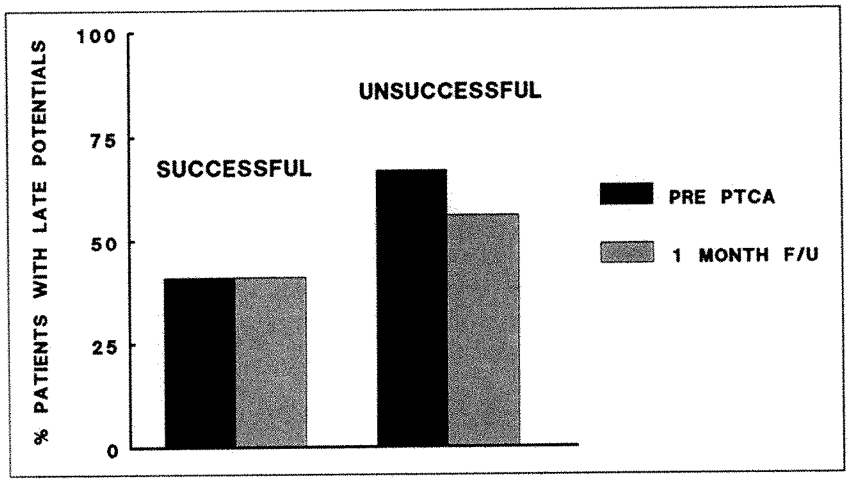

FIGURE 1. The effect of late reperfusion on the classification of the signal-averaged electrocardiogram. The percentage of patients with late potentials was the same before percutaneous transluminal coronary angioplasty (PTCA) *(solid bars)* and at 1-month follow-up (F/U) *(stippled bars)* in both the group of patients with successful (n = 32) and the group with unsuccessful (n = 9) reperfusion.

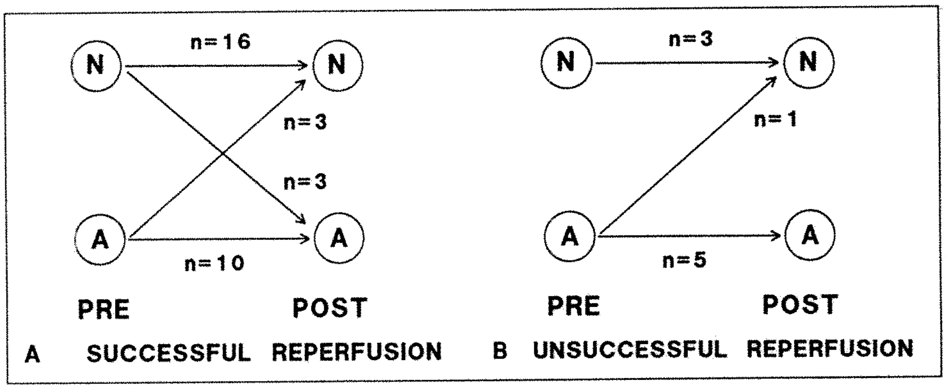

FIGURE 2. The effect of late reperfusion on the classification of the signal-averaged electrocardiogram in individual patients with successful *(A)* and unsuccessful *(B)* late reperfusion. As shown, few patients changed their signal-averaged electrocardiographic classification. A = abnormal; N = normal; POST = 1-month follow-up; PRE = baseline.

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viability as demonstrated by improved wall motion after successful reperfusion was associated with fewer late potentials at baseline before reperfusion but not with a further decrease in the prevalence of late potentials after successful reperfusion.

DISCUSSION

The present results demonstrate that reperfusion >24 hours after myocardial infarction did not alter the prevalence of late potentials on the SAECG. These results suggest that late reperfusion is not associated with a decrease in arrhythmia risk, or alternatively, any change in arrhythmia risk is not reflected by changes in the SAECG. After successful reperfusion, patients without late potentials improved regional function to a greater extent than did those with late potentials. Thus, the absence of late potentials appears to be associated with persistent myocardial viability.

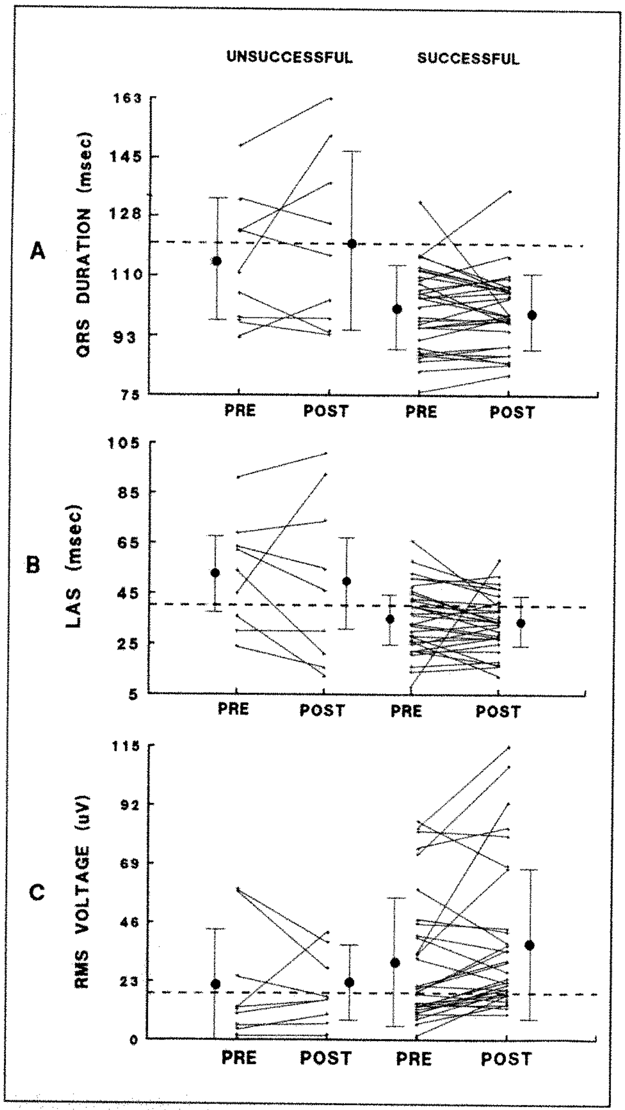

FIGURE 3. The effect of late reperfusion on the individual signal-averaged electrocardiographic parameters. Effect of successful reperfusion and unsuccessful reperfusion on QRS duration (in ms) *(A)*, terminal signal duration <40 μV (LAS) (in ms) *(B)*, and root-mean-square voltage (RMS) (in μV) *(C)*. *Dotted lines* indicate the limit of normal for each parameter. Other observations as in Figure 2.

Benefits of late reperfusion: Although there is a clear mortality benefit from reperfusion accomplished within 6 hours of the onset of acute myocardial infarction, the benefit of later reperfusion is uncertain. Several lines of evidence suggest that late reperfusion provides a survival advantage. Thrombolytic therapy as late as 24 hours after the onset of acute infarction may improve survival.[8,17] In addition, it appears that patency of the infarct-related artery even in the absence of early reperfusion is associated with a lower mortality than a persistently occluded artery.[10,11,18] These results suggest that late reperfusion (>24 hours after symptom onset) may improve survival. Because late reperfusion does not result in myocardial salvage, any mortality benefit would necessarily be due to other effects. Several benefits of late reperfusion have been proposed including improved ventricular function,[19] limitation of infarct expansion,[20] improved healing of the infarct zone[21] and perhaps an improvement in the electrophysiologic substrate of the myocardium.[9,10,22]

Early reperfusion decreases late potentials on the SAECG.[1–4] It has been suggested that this reflects a decrease in susceptibility to ventricular arrhythmias[12–14,23–26] and may at least partly explain the survival advantage conferred by early reperfusion. Similarly, a survival advantage of late reperfusion may be partly due to a decrease in susceptibility to serious ventricular arrhythmias, which might be reflected in less abnormalities on the SAECG. In contrast to this expectation, our data demonstrate that late reperfusion a mean of 12 days after infarction had no consistent effect on the SAECG even among patients in whom late reperfusion caused an improvement in regional ventricular function. The improvement in the root-mean-square voltage we observed could be explained as simply the natural history of the SAECG.[27–32] Whether or not the small change was due to reperfusion, it is unlikely that it has any clinical significance.

Relation between myocardial viability and late potentials: Patients with successful reperfusion and without late potentials improved wall motion more than those with late potentials. This suggests that one of the determinants of late potentials after acute myocardial infarction is the absence of viable myocardium in the infarction zone. Thus, a normal SAECG may be a marker of viability within the infarct zone.

Patients with subsequent unsuccessful reperfusion had a more abnormal QRS and terminal signal duration <40 μV at baseline than did those with successful reperfusion, consistent with the hypothesis that those with unsuccessful reperfusion had less viable tissue in the infarct zone than did those with successful reperfusion. One could speculate that a more complete infarction would be associated with both an abnormal SAECG and extensive microvascular disruption. In such patients, balloon dilation may not restore adequate flow and maintain vessel patency. Our data are consistent with this concept because in the 9 patients with unsuccessful angioplasty, 7 had the occlusion successfully crossed with a guidewire and balloon, but despite repeated inflations, adequate flow and persistent vessel patency were not achieved; in the other 2, an initially successful angioplasty was followed by subsequent reclosure confirmed by angiography.

Study limitations: Although most of the patients with successful reperfusion had improved thallium uptake in the infarct zone at 1 month (suggesting continued patency) and none had any symptoms or clinical events to suggest reclosure, we cannot be sure as to the continued patency of the infarct-related artery at 1 month in all patients because repeat angiography was not performed unless patients had a clinical event. However, the subgroup with successful reperfusion and improved thallium uptake at 1 month also had no change on the SAECG. This group almost certainly had persistent patency of the infarct-related artery. Another limitation may be in the time of recording of the initial SAECG. Because of evolutionary changes in the SAECG after myocardial infarction,[27-32] measurements performed at a different time might have given somewhat different results. Our study examined reperfusion very late after infarction. A study that focused on patients undergoing reperfusion 6 to 24 hours after infarction could yield different results. Finally, this study involves a relatively small number of patients. However, it is doubtful that enrolling a larger number of patients would substantially alter our chief findings since no convincing trend toward a favorable effect of reperfusion was discernible.

Acknowledgment: We thank Christine L. Tedesco, RN, for assistance in patient follow-up and data collection, and the staff of the electrocardiography laboratory of the University of Virginia Health Sciences Center for performance of the signal-averaged electrocardiography.

REFERENCES

1. Gang ES, Lew AS, Hong M, Wang FZ, Siebert CA, Peter T. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1989;321:712–716.

2. Chew E, Morton P, Murtagh JG, Scott ME, O'Keeffe DB. Intravenous streptokinase for acute myocardial infarction reduces the occurrence of ventricular late potentials. *Br Heart J* 1990;64:5–8.

3. Eldar M, Leor J, Hod H, Rotstein Z, Truman S, Kaplinsky E, Abboud S. Effect of thrombolysis on the evolution of late potentials within 10 days of infarction. *Br Heart J* 1990;63:273–276.

4. Pedretti R, Laporta A, Etro MD, Gementi A, Bonelli R, Anza C, Colombo E, Maslowsky F, Santoro F, Caru B. Influence of thrombolysis on signal-averaged electrocardiogram and late arrhythmic events after acute myocardial infarction. *Am J Cardiol* 1992;69:866–872.

5. Vatterott PJ, Hammill SC, Bailey KR, Wiltgen CM, Gersch BJ. Late potentials on signal-averaged electrocardiograms and patency of the infarct related artery in survivors of acute myocardial infarction. *J Am Coll Cardiol* 1991;17:330–337.

6. Rapaport E. Early versus late opening of coronary arteries: the effect of timing. *Clin Cardiol* 1990;13(suppl VIII):18–22.

7. Schröder R, Linderer T, Brüggemann T, Neuhaus KL, Tebbe U, Wegsheider K. Controversial indications: rationale for thrombolysis later than 4–6 h from symptom onset, and in patients with smaller myocardial infarctions. *Eur Heart J* 1990;11(suppl F):19–28.

8. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349–360.

9. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction and improved survival. Should the paradigm be expanded? *Circulation* 1989;79:441–444.

10. Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. *Am J Cardiol* 1989;64:155–160.

11. Abbottsmith CW, Topol EJ, George BS, Stack RS, Kereiakes DJ, Candela RJ, Anderson LC, Harrelson-Woodlief SL, Califf RM. Fate of patients with acute myocardial infarction with patency of the infarct-related vessel achieved with successful thrombolysis versus rescue angioplasty. *J Am Coll Cardiol* 1990;16:770–778.

12. Berbari EJ, Lazzara R. An introduction to high-resolution ECG recordings of cardiac late potentials. *Arch Intern Med* 1988;148:1859–1863.

13. Vatterott PJ, Hammill SC, Bailey KR, Berbari EJ, Matheson SJ. Signal- averaged electrocardiography: a new noninvasive test to identify patients at risk for ventricular arrhythmias. *Mayo Clin Proc* 1988;63:931–942.

14. Steinberg JS, Regan A, Sciacca RR, Bigger JT, Fleiss JL. Predicting arrhythmic events after acute myocardial infarction using the signal-averaged electrocardiogram. *Am J Cardiol* 1992;69:13–21.

15. Touchstone DA, Beller GA, Nygaard TW, Tedesco C, Kaul S. Effects of successful intravenous reperfusion therapy on regional myocardial function and geometry in humans: a tomographic assessment using two-dimensional echocardiography. *J Am Coll Cardiol* 1989;13:1506–1513.

16. Berger BC, Watson DD, Taylor GL, Craddock GB, Martin RP, Teates CD, Beller GA. Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease. *J Nucl Med* 1981;22:585–593.

17. European Cooperative Study Group. Streptokinase in acute myocardial infarction. *N Engl J Med* 1979;301:797–802.

18. Dalen JE, Gore JM, Braunwald E, Borer J, Goldberg RJ, Passamani ER, Forman S, Knatterud G, and the TIMI Investigators. Six- and twelve-month follow-up of the phase I Thrombolysis in Myocardial Infarction (TIMI) Trial. *Am J Cardiol* 1988;62:179–185.

19. Schröder R, Neuhaus KL, Linderer T, Brüggemann T, Tebbe U, Wegscheider K. Impact of late coronary artery reperfusion on left ventricular function one month after acute myocardial infarction (results from the ISAM study). *Am J Cardiol* 1989;64:878–884.

20. Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. *Circulation* 1987;1:299–306.

21. Hale SL, Kloner RA. Left ventricular topographic alterations in the completely healed rat infarct caused by early and late coronary artery reperfusion. *Am Heart J* 1988;116:1508–1513.

22. Sherry S, Marder VJ. Streptokinase and recombinant tissue plasminogen activator (rt-PA) are equally effective in treating acute myocardial infarction. *Ann Intern Med* 1991;114:417–423.

23. Gomes JA, Winters SL. The prognostic significance of the signal-averaged electrocardiogram in the infarct survivor. In: Current Topics in Cardiology. New York: Elsevier Science Publishing, 1991:423–437.

24. Gomes JA, Winters SL, Martinson M, Machac J, Stewart D, Targonski A. The prognostic significance of quantitative signal-averaged variables relative to clinical variables, site of myocardial infarction, ejection fraction and ventricular premature beats: A prospective study. *J Am Coll Cardiol* 1989;13:377–384.

25. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. *J Am Coll Cardiol* 1987;10:349–357.

26. Nalos PC, Gang ES, Mandel WJ, Landenheim ML, Lass Y, Peter T. The signal-averaged electrocardiogram as a screening test for inducibility of sustained ventricular tachycardia in high risk patients: a prospective study. *J Am Coll Cardiol* 1987;9:539–548.

27. Verzoni A, Romano S, Pozzoni L, Tarricone D, Sangiorgio S, Croce L. Prognostic significance and evolution of late ventricular potentials in the first year after myocardial infarction: a prospective study. *PACE* 1989;12:41–51.

28. Lewis SJ, Lander PT, Taylor PA, Chamberlain DA, Vincent R. Evolution of late potential activity in the first six weeks after acute myocardial infarction. *Am J Cardiol* 1989;63:647–651.

29. McGuire M, Kuchar D, Ganis J, Sammell N, Thorburn C. Natural history of late potentials in the first ten days after acute myocardial infarction and relation to early ventricular arrhythmias. *Am J Cardiol* 1988;61:1187–1190.

30. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: natural history and prognostic significance. *Circulation* 1986;74:1280–1289.

31. Turitto G, Caref EB, Mancina G, Fontaine JM, Ursell SN, El-Sherif N. Time course of ventricular arrhythmias and the signal-averaged electrocardiogram in the post-infarction period: a prospective study of correlation. *Br Heart J* 1988;60:17–22.

32. El-Sherif N, Ursell SN, Bekheit S, Fontaine J, Turitto G, Henkin R, Caref EB. Prognostic significance of the signal-averaged ECG depends on the time of recording in the postinfarction period. *Am Heart J* 1989;118:256–264.

Ventricular Arrhythmias in Rehabilitated and Nonrehabilitated Post–Myocardial Infarction Patients with Left Ventricular Dysfunction

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The incidence of ventricular arrhythmias in rehabilitated post–myocardial infarction (MI) patients with left ventricular dysfunction included in a long-term rehabilitation program was assessed and compared with that in similar patients who were not in such a program. Thirty-eight post-MI patients (2 to 19 years after the acute event) with ejection fraction $<40\%$ were investigated by 48-hour Holter monitoring. They were divided into the following 3 groups: group I, 11 patients who underwent arm training for 60 months; group II, 11 patients who underwent calisthenics for 36 months; and group III, 16 patients who were not in any rehabilitation program; the age of the patients was 61 ± 7, 61 ± 6 and 61 ± 9 years, respectively, ($p =$ not significant). Ejection fraction at rest was 31 ± 9 for group I, 29 ± 7 for group II, and 29 ± 7 for group III ($p =$ not significant). There were no significant differences concerning the location of MI, and antiarrhythmic treatment received by patients from all groups. At the conclusion of 48-hour Holter monitoring, 2 blood samples were obtained for assessment of norepinephrine (at rest and after postural change). Quality of life was determined by a detailed questionnaire, including questions concerning social activity, life satisfaction and sexual function. After 36 and 60 months, an improvement in hemodynamic condition of patients in group I was noted. Quality of life was higher in the rehabilitated patients, with enhanced emotional stability, satisfaction with work and social life, and a high percentage of return to work (82 vs 40%). The lowest levels of norepinephrine were found in group I and the highest in group III ($p <0.02$), whereas they were within normal limits in group II. Isolated ventricular premature beats (>60/hour) were found in 1 (10%), 2 (18%) and 9 (56%) patients ($p <0.05$), and complex ventricular arrhythmias in 4 (33%), 3 (27%) and 12 (77%) patients ($p <0.05$) in groups I, II and III, respectively. Nonsustained ventricular tachycardia was recorded in 2 patients (17%) from group I with 4 episodes, 2 patients (17%) from group II with 7 episodes, and 6 patients (37%) from group III with 24 episodes ($p <0.03$); 3 of the latter patients had complex ventricular arrhythmias also. It appears that a long-term comprehensive rehabilitation program decreases neuroadrenergic activity, the arrhythmogenic effect of catecholamines and consequently, the incidence of ventricular arrhythmias.

(Am J Cardiol 1993;71:24–27)

The effects of physical rehabilitation on patients with coronary artery disease and good left ventricular function has been thoroughly investigated.[1–6] Few data are available concerning post-myocardial infarction (MI) patients with impaired left ventricular function in long-term rehabilitation programs.[7–10] The aim of this retrospective study was to assess the incidence of ventricular arrhythmias in post-MI patients with left ventricular dysfunction in a long-term rehabilitation program and compare them with similar patients not in such a program.

METHODS

Forty-one post-MI patients (2 to 19 years after the acute event) with an ejection fraction $<40\%$ were included in the study. Patients with overt congestive heart failure, unstable angina, chronothropic incompetence, low-output syndrome, diastolic blood pressure >116 mm Hg, dissecting aortic aneurysm, recent systemic or pulmonary embolism, and active or recent thrombophlebitis were excluded from the study.

Patients were divided into the following 3 groups: group I, 11 patients who underwent arm training for 60 months; group II, 11 patients who underwent calisthenics for 36 months; and group III, 16 patients who were not in any rehabilitation program. Group I was the initial group of 11 post-MI patients with an ejection fraction $<40\%$ accepted for rehabilitation in 1984. Group II comprised post-MI patients accepted 24 months after the initial group. Group III comprised 16 consecutive post-MI patients examined in our outpatient clinic who fulfilled the aforementioned criteria for inclusion in the study, but were not referred for rehabilitation. All patients were in New York Heart Association functional class II or III without signs of overt congestive heart failure. The age of patients was 61 ± 7 years for group I,

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TABLE I Ventricular Arrhythmias Recorded in the Three Groups of Patients at the Beginning of the Study (A) and 24 Months Later (B)

	Group I (n)		Group II (n)		Group III (n)		
	A	B	A	B	A	B	p Value
Isolated VPBs (>60/hr)	1 (10%)	1 (10%)	2 (18%)	2 (18%)	9 (56%)	8 (50%)	<0.05
Complex VA	5 (45%)	4 (33%)	4 (33%)	3 (27%)	13 (81%)	12 (74%)	<0.05
Nonsustained VT	3 (27%)	2 (17%)	3 (27%)	2 (17%)	7 (43%)*	6 (37%)†	<0.03
No. of episodes	6	4	9	7	25	24	

*Four patients had complex ventricular arrhythmias also; †3 patients had complex ventricular arrhythmias also.
VA = ventricular arrhythmia; VPBs = ventricular premature beats; VT = ventricular tachycardia.

61 ± 6 for group II, and 61 ± 9 for group III (p = not significant [NS]). Ejection fraction at rest was 31 ± 9 for group I, 29 ± 6 for group II, and 29 ± 7 for group III (p = NS). There were no significant differences concerning the location of MI, diabetes mellitus, hypertension and antiarrhythmic treatment received by the 3 groups of patients. Power work capacity was comparable at the beginning of the study in the 3 groups of patients (71 ± 24, 71 ± 21 and 68 ± 23 in groups I, II and III, respectively; p = NS), as well as the rate pressure product (22,485, 19,492 and 21,880, respectively; p = NS).

All patients underwent a physical examination, routine blood tests, chest x-ray, 12-lead electrocardiography, symptom-limited exercise testing, exercise radionuclide ventriculography using technetium-99m, echo-Doppler, and 2 consecutive periods of 24-hour Holter monitoring. In addition, patients from group I also underwent cardiopulmonary testing. All patients underwent identical examinations at least once each year.

The arm training program consisted of arm ergometry (twice weekly), with an exercise period of 30 minutes' duration reaching 80% of ischemic heart rate. Calisthenic training was performed twice weekly, each session of 40 minutes' duration with an energy requirement of 2.2 to 7.8 Kcal • min.

After 24 months, 48-hour Holter monitoring was repeated in all patients from the 3 groups. At the end of the 48 hours of recording, blood was obtained for norepinephrine assessment with the patient at rest (supine) for 30 minutes and after postural change for another 5 minutes.

Norepinephrine was assessed by high-pressure liquid chromatography, using Bonpack C18 reverse-phase column and waters 460 electrochemical detector.[11] The results were expressed in pg/ml/plasma.

To assess quality of life, we used a questionnaire, including Wenger's[12,13] parameters, Karnowsky and Burchenal's[14] Performance Status Scale to measure physical condition and work capacity, and the Hospital Anxiety and Depression Scale[15] to measure emotional and psychological status. Questions concerning social activity and leisure time, life satisfaction, sexual function and self assessment were added to the initial questionnaire. For statistical analysis, we used the chi-square to assess the significance of differences in noncontinuous variables, and Student's *t* test to evaluate differences between paired mean values. Group data are reported as mean ± 1 SD, and the required level of significance was accepted at $p < 0.05$.[16]

RESULTS

After 36 and 60 months of arm training, power work capacity increased from 71 ± 21% to 78 ± 24%, and rate pressure product/100 from 168 ± 31 to 204 ± 51. Ejection fraction increased from 31 ± 8 to 34 ± 6 (p = NS) in group I and remained almost unchanged in groups II and III.

Reduction in active drug treatment was noted in 31, 26.6 and 13% of patients in groups I, II and III, respectively. Eight patients from group I who had angina pectoris at the onset of the training program were free of anginal pain at the conclusion of the program. A decrease in symptomatic treatment was also noted in 46, 44 and 13% of patients in groups I, II and III, respectively.

No fatality of any cause was observed during follow-up in the 3 groups of patients.

Quality of life: Thirty-three percent of patients in group III expressed fear and anxiety regarding their health in comparison with 13% in group II and 0% in group I. Satisfaction with work activity was reported in 73% of group II, 46% of group I and only 13% in group III. Fifty-three percent of patients in groups I and II were satisfied with their social life compared with 37% in group III. Physical activity, in addition to the rehabilitation program, was performed by 85, 73 and 53% of patients in groups I, II and III, respectively. A decrease in sexual function was reported in 73% of patients in group III; it was unchanged in 56% of group I and in 53% of group II. Eighty-two percent of patients in groups I and II returned to work; 64% of these were able to work full time compared with only 40% of those in group III (20% to part-time work).

Norepinephrine: The lowest levels of norepinephrine (227 ± 79 and 295 ± 54 pg/ml/plasma at rest and after provocation, respectively) were found in group I and the highest levels (373 ± 132 and 620 ± 233 pg/ml/plasma, respectively; $p < 0.02$) in group III, whereas in group II they were within normal limits (100 to 500 pg/ml/plasma) (270 ± 72 and 486 ± 265 pg/ml/plasma, respectively).

Ventricular arrhythmias recorded by 48-hour Holter monitoring (Lown and Wolf[17] classification) in the 3 groups of patients at the beginning of the study and 24 months later are detailed in Table I. Complex ventricular arrhythmias were defined as grade IVa or b arrhythmias. Nonsustained ventricular tachycardia was defined as ≥3 consecutive ventricular beats, with a heart rate >120 beats/min lasting <30 seconds.

The incidence of isolated ventricular premature beats and complex ventricular arrhythmias was less in groups I and II than in III ($p < 0.05$). The frequency of episodes of nonsustained ventricular tachycardia was also much less in groups I and II ($p < 0.03$). After an additional 24 months of training, the incidence of ventricular arrhythmias was even less in groups I and II, but remained almost unchanged in group III. The differences did not reach statistical significance.

DISCUSSION

In this study, isolated ventricular premature beats, complex ventricular arrhythmias and nonsustained ventricular tachycardia occurred most frequently in nonrehabilitated post-MI patients (group III), less frequently in those undergoing calisthenics (group II), and least often in those undergoing arm training (group I). In the latter group, an improvement in several parameters (power work capacity, rate pressure product and oxygen consumption) may reflect an amelioration of the hemodynamic condition of the patients. Eight patients in group I who had angina pectoris on admission to the study were free of angina at its conclusion. The consumption of drugs in general and of nitrates in particular were also reduced in the rehabilitated patients.

Quality of life was markedly improved in groups I and II. The rehabilitation program conferred to the patients confidence in their physical and psychological capacities, satisfaction with work and social life, and self-assurance. The data are in concordance with results obtained by Kellermann et al[18] in 55 post-MI patients followed in a 12-month rehabilitation program and with those reported by Dracup et al[19] who found that after 6 months of rehabilitation, 41 post-MI or post–coronary artery bypass graft patients were significantly less anxious and depressed, and had a better psychosocial adjustment.

In this study, norepinephrine levels were lowest in group I and highest in group III. Provocation of the sympathetic nervous system induced by postural change resulted in a 1.6-fold increase in norepinephrine in group III; in contrast, almost no increase occurred in group I and II. The results may reflect the higher emotional stability of patients in group I.

Cooksey et al[20] reported a decrease in plasma catecholamines at a given level of treadmill exercise after 3 months of training in 10 patients with ischemic heart disease. They suggested that there is a decreased sympathetic activity and catecholamine "sensitivity" in rehabilitated subjects.

Ehsani et al[21] found that after 12 months of intense exercise training, plasma catecholamines increased less at the same submaximal work rate in patients with coronary artery disease.

La Rovere et al[22] showed that physical training increases baroreflex sensitivity and decreases adrenergic input to the heart.

Podrid et al[23] showed that activation of the sympathetic nervous system is an important factor in the development of ventricular arrhythmias in patients with impaired ventricular function. Lown and Verrier[24,25] also emphasized the high correlation between neuroadrenergic activity and the appearance of life-threatening ventricular arrhythmias and sudden cardiac death.

In a recent report by Meredith et al[16] of 12 post-MI patients with left ventricular dysfunction who had sustained life-threatening ventricular arrhythmias outside the hospital 4 to 48 days before the study, it was found that total norepinephrine spillover into the circulation was 80% higher than that in a group of coronary artery disease patients without ventricular arrythmias, or in patients with chest pain and normal coronary arteries, or in healthy subjects.

The experimental studies of Verrier and Dickerson[27] showed that the behavioral response to anger and fear is characterized by consistent increases in heart rate, mean arterial blood pressure and plasma catecholamines levels, and a significant reduction in the repetitive extrasystolic threshold.

From our study, it appears that long-term exercise programs improve not only the hemodynamic and metabolic condition of patients, but also their emotional stability. The decreased levels of norepinephrine at rest and after provocation found in group I patients may reflect their positive psychological status, including a high satisfaction with social life and work, and a high reintegration into community life. These reduced levels of norepinephrine that showed no significant increase even after physiologic provocation may be due to decreases in neuroadrenergic activity and thus, the arrhythmogenic effect of catecholamines. The decreased incidence of complex ventricular arrhythmias and nonsustained ventricular tachycardia found in groups I and II after an additional 2 years of training may be more a result of emotional stability and improvement in psychosocial status than of improvements in hemodynamic and metabolic conditions.

Study limitations: The small number of patients, and the absence of randomization prevent any definitive conclusions concerning the effect of long-term rehabilitation programs in decreasing the incidence of ventricular arrhythmias in post-MI patients. Further studies are warranted to reach firm conclusions regarding the importance of exercise therapy in patients with impaired ventricular function and significant ventricular ectopy.

From the data, it appears that long-term rehabilitation programs may decrease neuroadrenergic activity, the arrythmogenic effect of catecholamines and consequently, the incidence of ventricular arrhythmias.

REFERENCES

1. Kellermenn JJ. Rehabilitation of patients with coronary heart disease. *Prog Cardiovasc Dis* 1975;18:303–329.
2. Letac B, Cribier A, Desplanches JF. A study of left ventricular function in coronary patients before and after physical training. *Circulation* 1977;56:375–378.
3. Jensen D, Atwood JE, Froelicher V, McKeman MD, Buttler A, Ashburn W, Ross J. Improvement in ventricular function during exercise studied with radionuclide ventriculography after cardiac rehabilitation. *Am J Cardiol* 1980;46:770–777.
4. Verani MS, Hartung GH, Hoepfel-Harris J, Welton DE, Pratt CM, Miller RR. Effects of exercise training on left ventricular performance in myocardial perfusion

in patients with coronary artery disease. *Am J Cardiol* 1981;47:797–803.

5. Hagberg JM, Ehsani AA, Holloszy JO. Effects of 12 months intensive training on stroke volume in patients with coronary artery disease. *Circulation* 1983;67:1194–1199.

6. Ehsani AA, Biello F, Schultz J, Sobel B, Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 1986;74:350–358.

7. Kellermann JJ, Ben Ari E, Fisman E, Hayet M, Drory Y, Haimovitz D. Physical training in patients with ventricular impairment. In: Kellermann JJ, Spodick DH, eds. Left Ventricular Dysfunction. Basel, Switzerland: Karger, 1986:131–147.

8. Tavazzi L, Ignone G, Giordano A, Giannuzzi P. Cardiac rehabilitation in patients with recent myocardial infarction and left ventricular dysfunction. In: Kellermann JJ, Spodick DH, eds. Left Ventricular Dysfunction. Basel, Switzerland: Karger, 1986:156–169.

9. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. *Circulation* 1988;75:506–515.

10. Kellermann JJ, Shemesh J, Fisman E, Steinmetz A, Ben-Ari E, Drory Y, Lapidot C. Arm exercise training in the rehabilitation of patients with impaired ventricular function and heart failure. *Cardiology* 1990;77:130–138.

11. Goldstein DS, Feuerstein G, Izzo J, Kopin I, Keiser H. Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in men. *Life Sci* 1981;28:467–475.

12. Wenger NK. Quality of life: concept and approach to measurement. *Adv Cardiol* 1986;33:122–130.

13. Wenger NK. Quality of life: can it and should it be assessed in patients with heart failure? *Cardiology* 1989;76:391–398.

14. Karnofsky D, Burchenal J. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. New York: Columbia University Press, 1949:191–205.

15. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361–370.

16. Bourke G, Gilweigh J. Interpretation and Uses of Medical Statistics. Oxford and Edinburgh: Blackwell Scientific, 1969:80–88.

17. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. *Circulation* 1971;44:130–142.

18. Kellermann JJ, Kariv I, Wintner I. Rehabilitation of coronary patients. Cardiac Evaluation and Rehabilitation Institute. Tel Hashomer, Israel: Segal Press Tel Aviv, 1968:53–75.

19. Dracup K, Moser DK, Marsden C, Taylor SE, Guzy PM. Effects of multidimensional cardiopulmonary rehabilitation program on psychosocial function. *Am J Cardiol* 1991;68:31–34.

20. Cooksey J, Reilly P, Bromse H, Cryer PE. Exercise training and plasma catecholamines in patients with coronary heart disease. *Am J Cardiol* 1978;42:371–376.

21. Ehsani AA, Heath GW, Martin WH III, Hagberg JM, Sobel B, Holloszy JO. Effects of intense exercise training on plasma catecholamines in coronary patients. *J Appl Physiol* 1984;57:155–163.

22. La Rovere MT, Specchia GT, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction. *Circulation* 1988;78:814–824.

23. Podrid EJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. *Circulation* 1990;82(suppl 2):I-103–I-113.

24. Lown B, Verrier RL. Neural activity and ventricular fibrillation. *N Engl J Med* 1976;294:1165–1170.

25. Lown B. Sudden cardiac death: the major challenge confronting contemporary cardiology. *Am J Cardiol* 1979;43:313–318.

26. Meredith IT, Broughton A, Jennings GL, Esler MD. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med* 1991;325:618–625.

27. Verrier R, Dickerson L. Autonomic nervous system and coronary blood flow changes related to emotional activation and sleep. *Circulation* 1991;83(suppl II):1181–1189.

Validation by High-Frequency Epicardial Echocardiography of a New Method of Analyzing Coronary Angiography Quantitatively in Coronary Artery Disease

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In coronary atherosclerosis, the arterial lumen size and shape can be markedly irregular, eccentric and variable. Traditional angiographic interpretation, emphasizing percent diameter stenosis, has been criticized as an inadequate descriptor of such diseased arteries. Computerized quantitative angiographic technologies, yielding a true lumen area measurement, may be superior. High-frequency epicardial echocardiography (HFEE) is a technique that allows on-line evaluation of coronary arterial wall and lumen at the time of cardiac surgery. It has been extensively validated and yields accurate measurements of normal and diseased coronary lumen areas. This study compares quantitative coronary angiography (QCA) estimates of lumen area to those obtained by HFEE to determine if the computerized angiographic method more accurately predicts residual luminal area than traditional angiographic percent diameter stenosis measurements. Although actual luminal morphology was quite variable, there was a good correlation between lumen areas determined by HFEE versus QCA: $r = 0.85$, $n = 67$, HFEE $= 0.8$ QCA $- 0.1$ (HFEE 4.0 ± 0.30 mm^2, mean $\pm$ SEM range 0.3 to 14.0; QCA 5.1 ± 0.40 mm^2, range 0.7 to 11.8). Percent diameter stenosis determined from the angiograms did not correlate well with HFEE or QCA measurements of residual luminal area. Separation of "normal" arterial segments (defined as <25% diameter stenosis) from "abnormal" segments (>50% diameter stenosis) by angiography did not agree with lumen areas as defined by either HFEE or QCA. Better separation occured when QCA-determined luminal areas were used to separate normal from abnormal arterial segments.

These data demonstrate that QCA accurately predicts residual luminal areas and indicate the inadequacy of traditional angiographic percent diameter stenosis measurements as an adequate descriptor of the presence and severity of coronary artery disease.

(Am J Cardiol 1993;71:28–32)

The traditional method of describing the severity of coronary atherosclerotic lesions is to determine percent luminal diameter narrowing (percent stenosis) from coronary angiograms. Percent stenosis relies on 2 incorrect assumptions: first, that the compared adjacent coronary artery is free of atherosclerotic disease; and second, the residual lumen is circular in shape so that a 1-dimensional luminal diameter can represent the cross-sectional area.[1] We and others[2–4] have, in fact, demonstrated that percent stenosis from angiography is a poor predictor of the extent of atherosclerotic coronary disease. Atherosclerosis alters residual lumen morphology causing residual lumen shapes from circular to oval to complex, limiting traditional percent stenosis for determining the importance of coronary lesions.[5–7]

High-frequency epicardial echocardiography (HFEE) is a new technique that can measure coronary lumen area directly at cardiac surgery. It has been well validated[8] and compares well with videodensitrometric estimates of coronary stenosis.[9]

Quantitative coronary angiography (QCA) is a computerized angiographic technique which may more accurately identify residual luminal area.[10,11] It also has been well validated with histologic measurements ex vivo and angiography but has not been compared with other nonangiographic techniques in vivo.

The purpose of this study was to compare HFEE luminal area measurements with those of a computerized quantitative coronary angiographic technique and with traditional estimates of angiographic "percent stenosis" We sought to determine if these angiographic techniques were adequate for detecting coronary atherosclerosis and were accurate in estimating the severity of coronary atherosclerotic narrowing.

METHODS

Intraoperative patient studies: This in vivo study was approved by the Human Use Committee at the Uni-

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From the Departments of Medicine and Engineering, Northwestern University Chicago, Illinois; and the University of Iowa, Iowa City, Iowa. This study was supported in part by Grants HL-14388, HL-00916, HL-43098 and HL-3295-05 from the National Heart, Lung and Blood Institute, Bethesda, Maryland; a grant from the Alberta Heritage Foundation for Medical Research, Alberta, Edmonton, Canada; and a grant from the Chicago Heart Association, Chicago, Illinois. Manuscript received February 24, 1992; revised manuscript received and accepted July 30, 1992.

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versity of Iowa. All patients gave written informed consent. Patients with known coronary artery disease undergoing open heart surgery for placement of coronary artery bypass grafts or undergoing other intracardiac procedures (valve replacement or atrial septal defect repair) were asked to participate. Coronary bypass operations were performed with a median sternotomy and standard operating procedure.

To minimize hemodynamic variability between intraoperative and catheterization data, all HFEE recordings were obtained 10 to 15 minutes before the initiation of cardiopulmonary bypass when the patient's hemodynamic status was stable. Systolic arterial pressures were >80 mm Hg for all data acquisition.

High-frequency echocardiography: IMAGING: A Surgiscan unit (Biosound Inc., Indianapolis) with a 12 MHz probe was used. This probe has a nominal axial resolution of 0.15 mm and a lateral resolution of 0.2 mm for 2-point structural resolution in a fixed system. In the operating room, the hand-held probe was slowly moved along the coronary artery to scan the artery, and then held stationary over selected diseased and normal areas during the recording of each image onto videotape. The location of each discrete segment of vessel visualized by HFEE was described by the surgeon, who noted the relation of the segment to major arterial branching points and estimated the distance from other landmarks such as the aortic root and cardiac apex. Each segment was also distinguished from other segments by major arterial branching points and morphologic landmarks. If the location of the echocardiographic image with regard to anatomic landmarks was uncertain, the image was not analyzed.

MEASUREMENTS: The HFEE images were digitized with an Irex Digitizing System (Irex Medical Systems). Only images with good wall, lumen and atherosclerotic plaque definition were used. Each image was displayed in cross section at that part of the cardiac cycle where the arterial diameter was largest to minimize variability due to coronary vasomotion. The luminal border was defined as the inner black/white interface. The luminal area was digitized and measured.

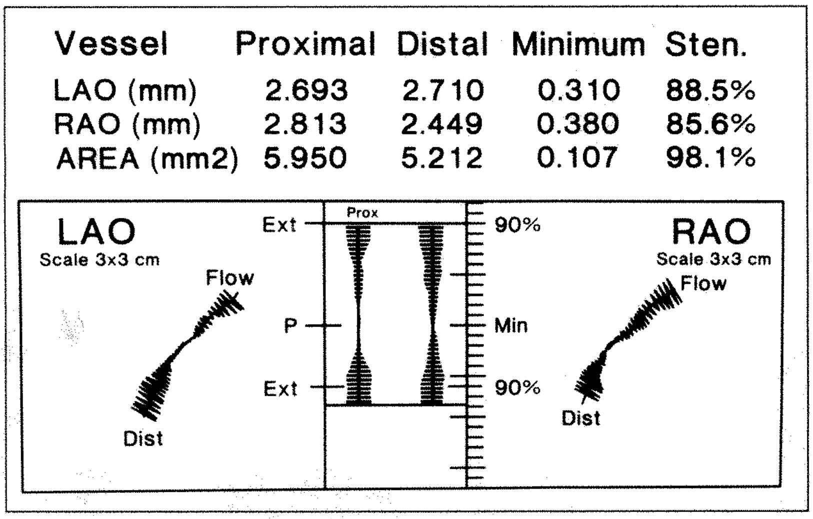
We avoided images from calcified arterial segments that often display "shadowing" and image loss posterior to the strongly ultrasound reflective calcifications and cannot be accurately traced. If luminal borders were not distinct for the 360° circumference, the videotape was played forward and back to completely identify arterial borders, and the indistinct few degrees of border were traced. If inadequate border definition was >30% of the arterial circumference, the data were excluded.

ANGIOGRAPHIC ANALYSIS: Preoperative cineangiograms were obtained using the Judkin's technique. All patients received atropine (0.6 mg subcutaneously) and nitroglycerin (0.4 mg sublingually) before angiography. Films were recorded at 60 frames/s, averaging 8 projections per patient. Cranial and caudal angulated views were obtained in the majority of cases. Only cineangiograms of high quality were analyzed.

In each case we attempted to identify the same coronary arterial segment imaged by HFEE and angiography, using the surgeons description of the HFEE probe placement and image acquisition and corresponding angiographic landmarks. Cineangiograms were reviewed by 2 independent observers for 2 purposes.

1. For qualitative estimation of percent stenosis and comparison with high-frequency echocardiographic images, the unprocessed cineangiograms were used. Lesions were identified angiographically as those areas with >50% narrowing by caliper measurement, compared with the immediate proximal segment.

2. For quantitative measurements of lumen area, the Brown-Dodge system of quantitative coronary arteriography[10,11] was used. Midcycle cine frames of orthogonal angiographic projections of the coronary segment to be analyzed were projected onto a large screen marked in rectilinear coordinants and the vessel segment was carefully traced. A portion of the angiographic catheter, of known size, was traced as a scaling factor. The position on the rectilinear grid of the catheter and of the vascular segment of interest were noted for each angiographic projection. The data from the 2 orthogonal views were digitized with a computer-interfaced Tektronix (Beaverton, Oregon) digitizing tablet. The steps used by the computer program to analyze each coronary segment have been previously described in detail.[10] Briefly, the x-ray magnification and pin-cushion distortion characteristics of the x-ray equipment were deter-



Vessel	Proximal	Distal	Minimum	Sten.
LAO (mm)	2.693	2.710	0.310	88.5%
RAO (mm)	2.813	2.449	0.380	85.6%
AREA (mm2)	5.950	5.212	0.107	98.1%

FIGURE 1. A quantitative coronary angiographic schematic. Proximal (Prox), distal (Dist) and minimal (Min) lesion diameters and areas and percent stenosis (Sten.) are calculated. Ext = external; LAO = left anterior oblique; P = plaque; RAO = right anterior oblique.

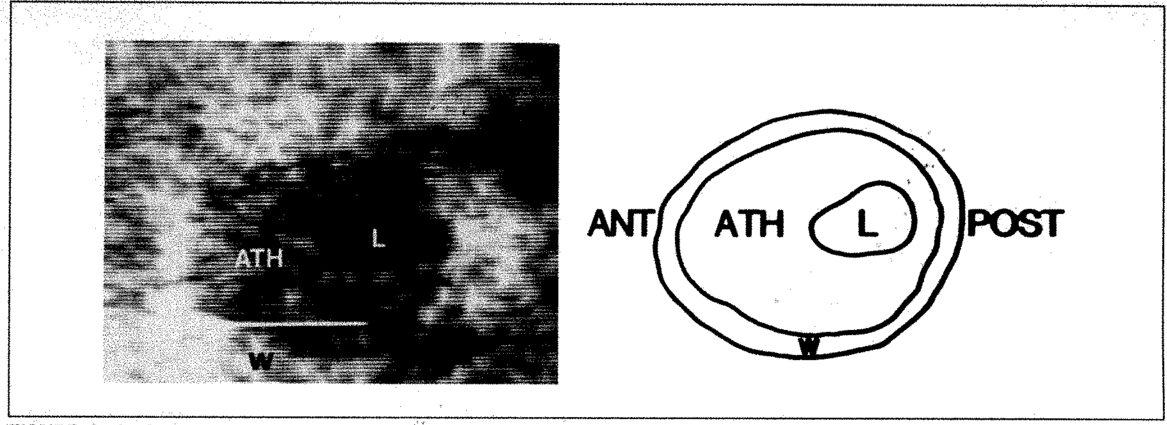


FIGURE 2. An intraoperative high-frequency epicardial echocardiographic image of a coronary arterial lesion in cross section *(left panel)* and corresponding diagram *(right panel)*. Reference bar = 3 mm; ANT = anterior; ATH =atherosclerotic plaque; L = arterial lumen; POST = posterior; W = arterial wall.

mined and entered into the computer. Each view was then corrected for magnification and pin-cushion distortion. The center lines of the vessel in each view were matched and a 3-dimensional reconstruction of the vascular segment of interest was created. The computer calculated the absolute cross-sectional area of the vascular segment of interest and the percent luminal diameter stenosis measurement for the segment in each orthogonal view. The analysis was repeated for 3 consecutive paired angiographic frames per coronary segment. The average values of the determinations of cross-sectional area and percent diameter stenosis for the 3 sets of frames were calculated and reported as segment cross-sectional area and percent diameter stenosis. Figure 1 illustrates the quantitative coronary angiographic schematic.

Protocol: COMPARISON OF CORONARY ARTERIAL LUMINAL AREAS BY QUANTITATIVE CORONARY ANGIOGRAPHY AND HIGH-FREQUENCY EPICARDIAL ECHOCARDIOGRAPHY: In vivo HFEE segments (68) having a wide range of luminal geometries varying from relatively normal to abnormal were used. For each segment, from 4 to 10 echocardiographic images were displayed in cross section and luminal area derived throughout the segment evaluated. A mean segmental area was derived for each specific arterial segment and this was compared with that derived using QCA and with percent stenosis.

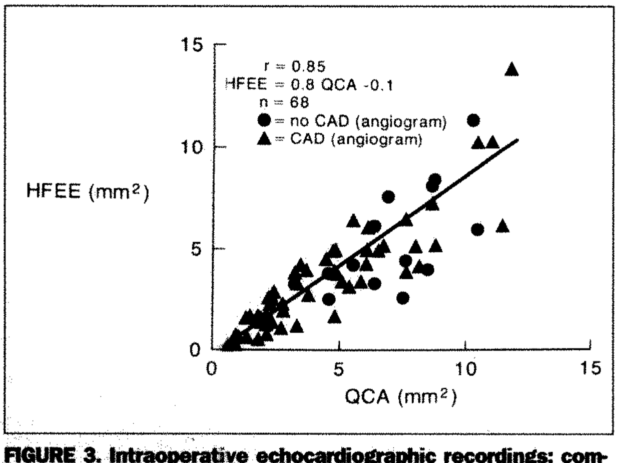


FIGURE 3. Intraoperative echocardiographic recordings: comparison between luminal areas measured by high-frequency epicardial echocardiography (HFEE) and quantitative coronary angiography (QCA). There is a good relationship between the 2 measurements. CAD = coronary arterial disease.

STATISTICAL ANALYSIS: Paired or unpaired *t* tests were used as appropriate to evaluate the data sets. Differences were considered significant when confidence limits exceeded 95% ($p < 0.05$). All results are expressed as mean ± SEM.

RESULTS

Figure 2 illustrates a high-frequency echocardiographic image of a coronary arterial segment in cross section. Table I lists patient characteristics for the HFEE/QCA comparisons. Twenty-four men and women were studied with approximately two third of the group having angiographic and one third having no angiographic evidence of coronary disease, but undergoing other intracardiac procedures (valve replacement or atrial septal defect repair). In each patient, from 1 to 6 segments were compared by both HFEE and QCA. The segments evaluated were in either the proximal or mid-portion of the right or left anterior descending coronary arteries.

Figure 3 illustrates the comparisons between mean luminal areas for the coronary arterial segments evaluated by QCA and HFEE. For comparison purposes, ar-

TABLE I High-Frequency Echocardiography Versus Quantitative Coronary Angiography for Luminal Evaluation

Patient Characteristics	Men	Women
No angiographic coronary disease	4	5
Angiographic coronary disease	9	6
Total	13	11
Age (year) of total group		
Mean (range)	57 (36–72)	52 (19–76)
Coronary arterial segments evaluated (mean per patient/range)	2.8/1–6	
Right coronary artery		
Proximal	20	
Mid	14	
Distal	7	
Left anterior descending coronary artery		
Proximal	11	
Mid	14	
Distal	1	

terial segments evaluated in which there was minimal angiographic evidence of coronary disease (i.e., <25% angiographic narrowing in any vessel in the coronary arterial tree) are displayed as circles. Arterial segments evaluated from patients having evidence of coronary arterial disease by angiography (>50% stenosis) are displayed as triangles. There was a good correlation between HFEE and QCA measured luminal areas over the wide range of contrary arterial segments from normal to markedly stenotic (r = 0.85; HFEE = 0.8 QCA – 0.1). The regression line is especially close to unity for the small luminal areas but there is scatter for the moderate and large luminal areas. Mean luminal areas were HFEE (4.0 + 0.30 mm^2 [mean ± SEM]), (range 0.3 to 14.0); and QCA (5.1 + 0.40 mm^2), (range 0.7 to 11.8).

Figure 4 illustrates luminal areas divided into groups based on "percent stenosis" identified by caliper measurements from the coronary angiogram. In each group, angiographically "normal" segments with <25% percent stenosis are on the left. When independently assessed by HFEE and QCA, there was considerable overlap of mean luminal areas for segments with and without disease as judged by angiographic percent stenosis measurements.

Figure 5 illustrates luminal areas divided into groups based on QCA percent stenosis. Angiographic normal segments are on the left and "50% QCA luminal area stenosis" segments are on the right. QCA better separated normal from abnormal luminal areas than did caliper percent stenosis measurements.

DISCUSSION

We have shown that traditional angiographic percent stenosis measurements do not accurately reflect reductions in arterial lumen area when coronary atherosclerosis is present. Percent stenosis could not completely separate luminal area measurements from arteries with only minimal disease (<25% stenosis) from those with severe atherosclerosis. Quantitative coronary angiographic measurements of luminal areas more closely correlated with another in vivo technique — HFEE — and was able to better seperate segments with minimal stenosis from those with severe atherosclerosis.

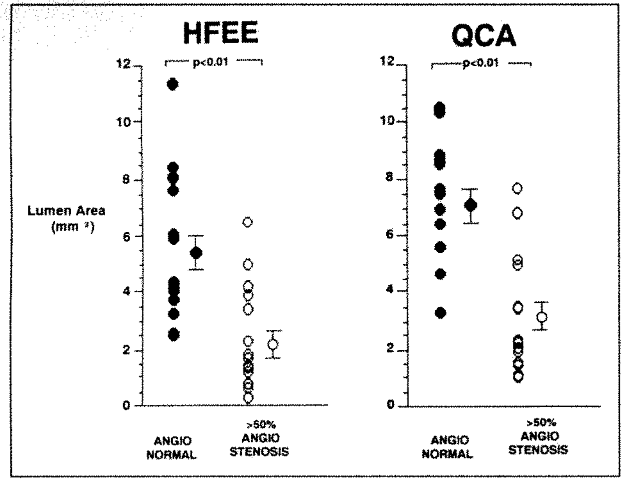


FIGURE 4. Comparison of luminal areas by both high-frequency epicardial echocardiography (HFEE) and quantitative coronary angiography (QCA) subdivided by "percent stenosis" measurements from the standard coronary angiograms. The percent stenosis measurements failed to separate normal from substantially diseased arteries when disease was independently assessed either by HFEE or QCA; considerable overlap is seen in *both panels*. ANGIO = angiogram/angiographic.

Marked variability in atherosclerotic plaque size and shape is characteristic of atherosclerotic lesions.[5] Nearly half of atherosclerotic lesions are noncircular in shape.[12] In such irregular lumens, descriptors of luminal geometry using a 1-dimensional technique such as percent stenosis would be inaccurate, as we found.

Although QCA has been a well-validated technique,[10,11] it shares with traditional percent stenosis assumptions that do not accurately reflect the nature of coronary atherosclerosis. With QCA, luminal areas are calculated from 2 single dimension measurements. The first assumption is that there are no or only insignificant irregularities of the atherosclerotic plaque around the luminal circumference. The second assumption is that maximal and minimal diameters are always used, if there is an oval lumen. The third assumption is that minimal luminal diameters are exactly superimposed. These assumptions could be incorrect since a large percentage of lesions have oval or noncircular residual lumens and there is variable luminal morphology throughout the lesion.[12] Thus, superimpositions and identifications of minimal and maximal diameter may be erroneous. Nevertheless, we found good agreement between HFEE and QCA over a large range of lumens and lesions.

Percent angiographic diameter stenosis measurements correlate poorly with true luminal estimates. In this study >1/3 of the luminal areas of segments having angiographically significant disease (i.e., >50% diameter stenosis) had areas within the normal range determined by either HFEE or QCA. Thus, angiographic estimates of percent stenosis may not accurately separate normal from abnormal coronary arterial segments, and may not accurately reflect the presence of coronary atherosclerosis.

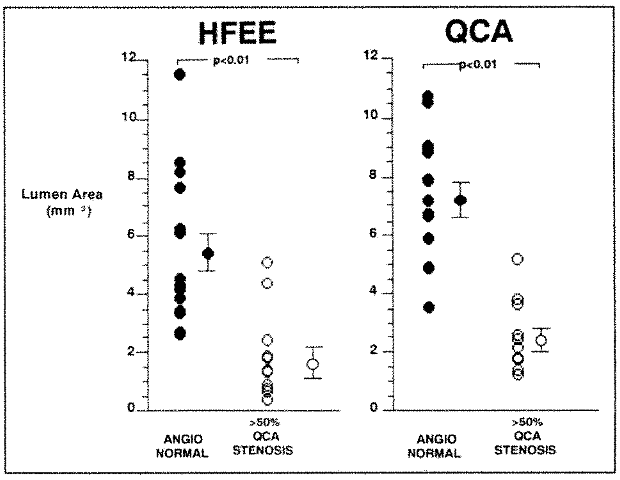


FIGURE 5. Comparison of luminal areas by both high-frequency epicardial echocardiography (HFEE) and quantitative coronary angiography (QCA) subdivided by "percent area stenosis" measurements from the quantitative coronary angiograms (ANGIO). Percent area stenosis by this quantitative angiographic method better separated normal from substantially diseased arteries. Compare with Figure 4.

QCA determined luminal stenosis measurements seem to separate more accurately normal from abnormal coronary segments. Although validated histologically and by other in vivo angiographic techniques, this is the first in vivo study to validate its accuracy using a nonangiographic imaging technique. HFEE, a real-time technique has been shown to be accurate for measuring normal and diseased lumen areas, in both animal and human studies.[8] It demonstrates arterial disease which is often not apparent or underestimated by traditional techniques. It has been previously compared with videodensitometric coronary angiographic analytic techniques with good correlation.[9] It is a suitable comparison and validation method for the 2 angiographic techniques used.

If vessels of varying size from large (i.e., proximal right coronary artery) to small (i.e., obtuse marginal or diagonal branches) had been studied, it would be unreasonable to expect a correlation between absolute lumen area and percent stenosis by angiographic estimates. We restricted our analysis to large (proximal and mid right and left anterior descending) coronary arteries to avoid this problem.

Errors may have occurred when matching the luminal area and lesion by HFEE and QCA. These may be due to data angulation, calcification with ultrasound drop-out and differing times of data acquisition with hemodynamic variability. In general, these factors would tend to occur randomly and may account for some of the minor discrepancies between HFEE and QCA measurements.

We have demonstrated that QCA, despite reliance on certain assumptions that do not accurately reflect the nature of coronary atherosclerosis, can determine the size of atherosclerotic lumens. Angiographic percent diameter stenosis measurements are frequently inaccurate in defining the presence and extent of coronary atherosclerosis.

Acknowledgment: We acknowledge the assistance of Berkeley Brandt, MD, Loren Hiratzka, MD, and Wade Lamberth, MD, in acquiring the intraoperative data, and the expert manuscript preparation of Jean Waller.

REFERENCES

1. Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DG, Kerber RE. Visual estimates of percent diameter coronary stenosis: "a battered gold standard." *J Am Coll Cardiol* 1988;11:882–885.

2. McPherson DD, Hiratzka LF, Lamberth WC, Brandt B, Hunt M, Kieso RA, Marcus ML, Kerber RE. Delineation of the extent of coronary atherosclerosis by high frequency epicardial echocardiography. *N Engl J Med* 1987;316:304–309.

3. Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, Roberts WC. Coronary artery narrowing in coronary heart disease: Comparison of cineangiographic and necropsy findings. *Ann Intern Med* 1979;91:350–356.

4. Vlodaver Z, Frech R, VanTassel RA, Edwards JE. Correlation of the antemortem coronary arteriogram and the postmortem specimen. *Circulation* 1973;47:162–169.

5. Waller BF. The eccentric coronary atherosclerotic plaque: morphologic observations and clinical relevance. *Clin Cardiol* 1989;12:14–20.

6. Freudenberg H, Lichtlen PR. The normal wall segment in coronary stenosis — a postmortal study. *Z Kardiol* 1981;70:863–868.

7. Saner HE, Gobel FL, Salamonowitz E, Erlien DA, Edwards JE. The disease — free wall in coronary atherosclerosis: its relation to degree of obstruction. *J Am Coll Cardiol* 1985;6:1096–1099.

8. McPherson DD, Armstrong M, Rose E, Kieso RA, Megan M, Hunt M, Hite P, Marcus HL, Kerber RE. High frequency epicardial echocardiography for coronary artery evaluation: in vitro and in vivo validation of arterial lumen and wall thickness measurements. *J Am Coll Cardiol* 1986;8:600–606.

9. Johnson MR, McPherson DD, Fleagle SR, Hunt MM, Hiratzka LF, Kerber RE, Marcus ML, Collins SM, Skorton DJ. Videodensitrometric analysis of human coronary stenosis: validation in vivo by intraoperative high frequency epicardial echocardiography. *Circulation* 1988;77:328–336.

10. Brown BG, Bolson EL, Frimer M, Dodge HT. Quantitative coronary arteriography: estimation of dimensions, hemodynamic resistance and atheroma mass of coronary artery lesions using the arteriogram and digital computation. *Circulation* 1977;55:329–337.

11. Brown BG, Bolson EL, Dodge HT. Arteriographic assessment of coronary atherosclerosis: review of current methods, their limitations and clinical applications. *Atherosclerosis* 1982;2:2–15.

12. McPherson DD, Johnson MR, Alvarez NM, Rewcastle NB, Collins SM, Armstrong ML, Kieso RA, Thorpe LJ, Marcus ML, Kerber RE. Variable morphology of coronary atherosclerosis: characterization of atherosclerotic plaque and residual arterial lumen size and shape by epicardial echocardiography. *J Am Coll Cardiol* 1992;19:593–599.

Prognostic Value of Dobutamine Echocardiography in Patients with High Pretest Likelihood of Coronary Artery Disease

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To examine the value of transient regional asynergy on dobutamine stress echocardiography as a noninvasive predictor of future cardiac events, 51 symptomatic patients (aged 54 ± 9 years) with suspected coronary artery disease (CAD) were studied using an incremental regimen of 5, 10, 15 and 20 µg/kg/min. Pretest likelihood of CAD was (mean ± standard error of the percentage) 79.7 ± 5.6% before and 83.4 ± 5.2% after exercise electrocardiography using probability analysis based on age, sex and symptoms. Two-dimensional images were analyzed with reference to an 11-segment model and gave good interrater agreement. During 24 ± 4 months (range 19 to 32) of follow-up, 23 patients had events (1 myocardial infarction, 9 unstable angina, 10 coronary bypass surgery, 3 coronary angioplasty) and 28 were event free. Age, proportion with baseline asynergy and both pretest echocardiographic ejection fraction and its response to dobutamine were similar in these 2 groups (all p = not significant). Transient asynergy was seen in 17 of 23 patients (74%) with and 8 of 28 patients (29%) without events ($p < 0.01$); 5 of 6 patients (83%) with involvement of 3 segments had events. Myocardial infarction or unstable angina occurred in 8 of 25 (32%) with a positive and 2 of 26 (8%) with a negative stress echocardiogram ($p < 0.05$). Both exercise duration (389 ± 195 vs 517 ± 237 seconds, $p < 0.05$) and time to diagnostic ST-segment shift (291 ± 192 vs 447 ± 212 seconds, $p = 0.05$) were shorter in those with inducible asynergy. These data suggest that patients with probable CAD and a positive dobutamine echocardiogram are at higher risk of an adverse outcome. Dobutamine echocardiography may aid selection for coronary angiography and prognostic revascularization, particularly in patients unable to exercise.

(Am J Cardiol 1993;71:33–39)

Noninvasive identification of patients with known or suspected coronary artery disease (CAD) who are at increased risk of future cardiac events guides patient selection for coronary angiography.[1] Prognosis is influenced by many variables including evidence of inducible myocardial ischemia which implies underlying flow-limiting CAD and jeopardized myocardium and is conventionally sought using exercise electrocardiography.[2] However, ST-segment analysis has limitations as a marker of ischemia because of not infrequent false-positive, equivocal or uninterpretable results, particularly in patients with abnormal rest ST segments. Clinical and experimental evidence suggests that transient regional asynergy on stress 2-dimensional echocardiography provides a more sensitive and specific diagnostic end point than electrocardiographic criteria.[3–5] Exercise echocardiography enables risk stratification of patients after uncomplicated myocardial infarction[6–8] but cannot be performed in those unable or poorly motivated to exercise. Dobutamine echocardiography, an alternative approach in these cases, has emerged as a safe and accurate method of detecting CAD[9,10] but its usefulness in prognostication has not been reported. Improved image quality and easier image acquisition are further advantages of this test and arise because patients are at rest, optimally positioned and able to suspend respiration if necessary. We therefore prospectively investigated the prognostic value of dobutamine echocardiography versus exercise electrocardiography in patients with high pretest probability of CAD and correlated the findings with coronary angiographic data.

METHODS

Study patients: We screened 55 consecutive symptomatic patients with suspected CAD awaiting coronary angiography who satisfied the study enrollment criteria. Patients with impaired left ventricular function (ejection fraction <30%), ventricular arrhythmias, unstable angina or uncontrolled systemic hypertension were excluded as were those with additional cardiac diseases including valvular or congenital heart disease or cardiomyopathy. To optimize the comparison of electrocardiography with echocardiography patients taking digoxin or those with bundle branch block, nonisoelectric rest ST segments or extensive baseline regional asynergy were considered unsuitable. Four patients were excluded because of poor endocardial definition on transthoracic imaging at baseline (test feasibility 93%). The remaining 51 patients (45 men and 6 women, mean age ± SD 54 ± 9 years, range 28 to 69) all had sinus rhythm and underwent both dobutamine and exercise tests after discontinuing car-

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TABLE I Comparison of Clinical and Investigative Variables in Relation to Event Status

	Cardiac Event (n = 23)	No Cardiac Event (n = 28)
Age (year)	55 ± 8	54 ± 10
Men/women	21/2	24/4
Symptoms		
Typical angina/atypical angina/NCP	19/4/0	21/5/2
Treatment*		
β blockers	16	13
Aspirin	14	9
Hypertension	5	7
Abnormal baseline electrocardiogram	12	10
Baseline regional asynergy†	8	6
Baseline ejection fraction (%)†	56 ± 6	58 ± 8
Follow-up duration (months)	24 ± 5	24 ± 3

*Numbers of patients receiving continuous treatment during follow-up.
†From 2-dimensional echocardiography.
NCP = noncardiac pain.

dioactive treatment for 4 half-lives. Pretest likelihood of CAD, expressed as mean ± SE of the percentage, and determined using probability analysis based on age, sex and symptoms by consulting tables published by Diamond and Forrester,[11] was 79.7 ± 5.6% before and 83.4 ± 5.2% after exercise electrocardiography. Forty patients had typical angina, 9 atypical angina and 2 noncardiac pain, and 14 patients had historic and echocardiographic evidence of previous myocardial infarction. The study protocol was approved by the hospital ethics committee. All patients gave informed consent.

Dobutamine echocardiography: With the patient reclining in the left semilateral position, baseline hemodynamic, electrocardiographic and echocardiographic data were initially collected. Under continuous monitoring, dobutamine was then infused into a peripheral vein using an incremental regimen of 5, 10, 15 and 20 μg/kg/min, each dose for 8 minutes. A 12-lead electrocardiogram and heart rate and blood pressure readings (Dinamap vital signs monitor, Critikon) were obtained every 1 to 2 minutes. Two-dimensional echocardiography (Toshiba SSH-160A, 3.75 MHz transducer) using the parasternal long-axis, short-axis and apical 4- and 2- chamber views was continuous for up to 20 minutes after dobutamine administration. Images were recorded on 12 mm VHS videotape and subsequently interpreted in a blinded manner by 2 independent experienced observers; disagreements were resolved by discussion. Wall motion, graded as hyperkinetic, normal, hypokinetic, akinetic or dyskinetic, was assessed at baseline and peak stress with reference to a previously described 11-segment model of the left ventricle.[5] A normal dobutamine echocardiogram was recorded as one in which all segments normal at baseline showed a hyperdynamic response, whereas the development of new or worsening regional asynergy was considered abnormal.[12] Study end points included clear echocardiographic or electrocardiographic evidence of ischemia, significant symptoms or arrhythmia, target heart rate (85% of 220 minus age in years), symptomatic hypotension or completion of the protocol. Percent ejection fraction was calculated at baseline and peak stress from end-diastolic and end-systolic frames of apical and parasternal short-axis views using a modified Simpson's rule algorithm.[13] Baseline, inter- and intraobserver variabilities of echocardiographic ejection fraction were each determined from 20 pairs of observations. Because the diagnostic and prognostic value of dobutamine echocardiography was unknown at the time of the study, managing physicians were not routinely informed of the results.

Exercise electrocardiography: All patients had a maximal modified Bruce treadmill exercise electrocardiogram using a computerized ST-segment analysis system (case 12, Marquette) and conventional end points.[14] A hypotensive response to exercise or dobutamine was defined as a ≥20 mm Hg decrease in systolic blood pressure during stress. Both exercise and dobutamine electrocardiograms were interpreted in an unbiased manner and were considered positive for ischemia if there was ≥1 mm of new onset ST elevation or nonupsloping ST depression 80 ms after the J point in any lead on 3 consecutive beats. No cardiac events occurred between dobutamine echocardiography, exercise testing and coronary angiography, which were performed within 3 weeks of each other in all patients.

Cardiac catheterization: Selective coronary arteriography was performed using multiple views and a Philips Poly Diagnost C imaging system. Angiograms were evaluated from 35 mm cinefilm by an observer unaware of the other results and were classified as normal, showing minor lesions or coronary stenoses in a major epicardial vessel that reduced diameter by ≥50%.

Follow-up: Follow-up data were obtained over a 24 ± 4 month (range 19 to 32) period by outpatient clinic assessment, telephone interview, review of case notes and contacting other hospitals when necessary. Outcome events were cardiac death, nonfatal myocardial infarction and unstable angina necessitating hospitalization (hard events) and also coronary bypass surgery or transluminal angioplasty. For survival analysis only 1 event was counted in each patient and therefore any subsequent event(s) was not considered. The observation period was censored at last assessment in event-free patients and in those lost to follow-up.

Statistical analysis: Except where indicated, values are summarized as mean ± SD. Kaplan-Meier curves were plotted to summarize follow-up data and compared using the log-rank test and hazard ratio with 95% confidence interval.[15] Continuous variables were compared using a *t* test or equivalent nonparametric test as appropriate. The chi-square test with Yates' correction and McNemar's test were also used where indicated. Interrater agreement was determined by calculating the kappa coefficient without weighting and its 95% confidence interval.[16] Variability is expressed as percent coefficient of variation. A p value <0.05 was considered statistically significant.

RESULTS

Clinical outcome: During follow-up, 23 patients had 1 (n = 16) or 2 (n = 7) cardiac events. First events were myocardial infarction in 1, unstable angina in 9, coronary bypass grafting in 10 and coronary angioplasty in 3, and occurred after 9.3 ± 7.5 months (range 1 to

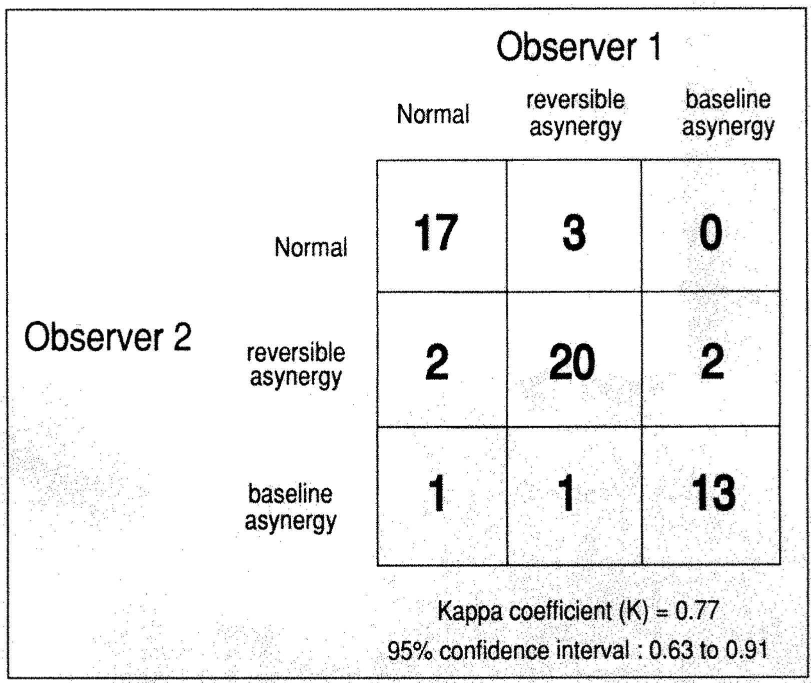
TABLE II Dobutamine Echocardiography and Electrocardiography, and Exercise Testing Variables as Predictors of Cardiac Events

	Cardiac Event (n = 23)	No Cardiac Event (n = 28)	p Value
Dobutamine echocardiography			
Positive test	17	8	0.003
Angina	9	5	NS
Infusion duration (min)	25 ± 7	26 ± 7	NS
Time to WMA (min)	20 ± 6	19 ± 5	NS
Peak HR (beats/min)	114 ± 20	118 ± 19	NS
Peak HR × SBP (mm Hg/min)	18,699 ± 4,461	18,946 ± 3,887	NS
Dobutamine electrocardiography			
Positive test	11	9	NS
Time to ST shift (min)	19 ± 6	18 ± 6	NS
Exercise electrocardiography			
Positive test	19	12	0.009
Angina	14	9	NS
Exercise duration (sec)	378 ± 154	517 ± 256	0.03
Time to ST shift (sec)	286 ± 176	429 ± 234	0.06
Peak HR (beats/min)	134 ± 26	145 ± 24	NS
Peak HR × SBP (mm Hg/min)	21,327 ± 4,518	24,658 ± 6,656	NS

HR = heart rate; SBP = systolic blood pressure; WMA = wall motion abnormality.

25) of observation. Second events were unstable angina in 1, coronary bypass surgery in 4 and coronary angioplasty in 2; no patient died during follow-up. As a rule, revascularization was undertaken for persistent or worsening symptoms despite medical treatment, although there were additional prognostic grounds in 9 instances. At last review of these 23 patients, 5 were asymptomatic and chest pain was either better (n = 14) or unchanged (n = 4) in the remaining patients. One event-free patient was lost to follow-up after 19 months observation. At censoring, 6 patients were asymptomatic and chest pain was better in 11, unchanged in 8 and worse in 3. One patient refused revascularization.

Patient data: Table I shows that baseline clinical and investigative variables were similar in patients with and without subsequent cardiac events (all p = NS). The predominant electrocardiographic abnormality was pathologic Q waves in 10, T-wave changes in 7 and left ventricular hypertrophy in 5. Infarct location on 2-dimensional echocardiography was inferior (n = 6), anteroseptal (n = 4), apical (n = 2) or lateral (n = 2) and involved 19 and 17 segments, respectively, in patients with and without events (p = NS). Adequate endocardial definition enabled precise calculation of ejection fraction in 33 patients (65%) and was 57 ± 7% (range 36 to 68); an ejection fraction range was assigned to the others (30 to 44%, n = 2; 45 to 55%, n = 6; 56 to 75%, n = 10). Baseline, inter- and intraobserver variability of ejection fraction was 10, 9 and 7%, respectively. The respective numbers of patients with normal



Observer 1

Observer 2	Normal	reversible asynergy	baseline asynergy
Normal	17	3	0
reversible asynergy	2	20	2
baseline asynergy	1	1	13

Kappa coefficient (K) = 0.77

95% confidence interval : 0.63 to 0.91

FIGURE 1. Interobserver agreement for wall motion analysis.

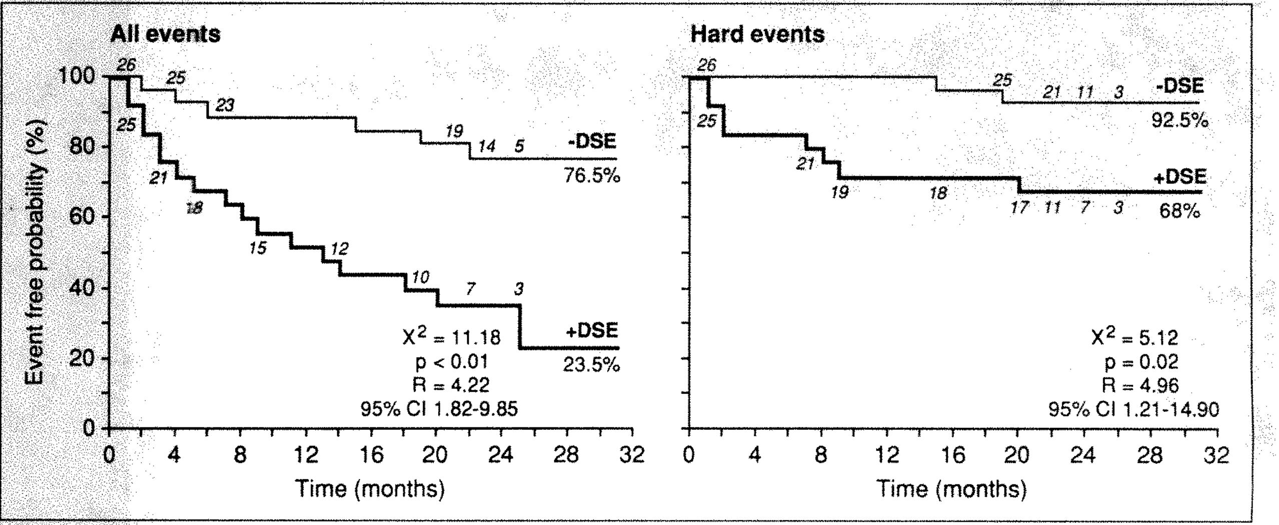


FIGURE 2. Kaplan-Meier curves for all *(left)* and hard *(right)* cardiac events during follow-up by results of dobutamine stress echocardiography (+DSE or −DSE). Each *plot* represents the cumulative proportion of patients remaining event free. *Numbers on the graphs* indicate the total number of patients remaining at risk. CI = confidence interval; R = hazard ratio.

coronary arteries, minor lesions or 1-, 2- or 3-vessel disease were 0, 0, 5, 7 and 11 in patients with events and 8, 6, 7, 4 and 3 in those who were event free ($p < 0.01$).

Dobutamine stress testing: Dobutamine infusion was well tolerated and without significant complications. Mean peak heart rate (116 ± 20 beats/min) and double product (18,834 ± 4,115 mm Hg/min) attained and the proportion reaching target heart rate (4 of 23 vs 5 of 28, p = NS) were not helpful as predictors of cardiac events (Table II). A hypotensive response to dobutamine stress (2 of 23 vs 5 of 28, p = NS) was similarly nondiscriminatory. Interrater agreement for wall motion analysis is shown in Figure 1. New (n = 22) or worsening (n = 1) regional asynergy, or both (n = 2) involving 1 (n = 7), 2 (n = 12) or 3 (n = 6) segments was seen in 25 patients; the worst segment was graded as hypokinetic in 2, akinetic in 17 and dyskinetic in 6.

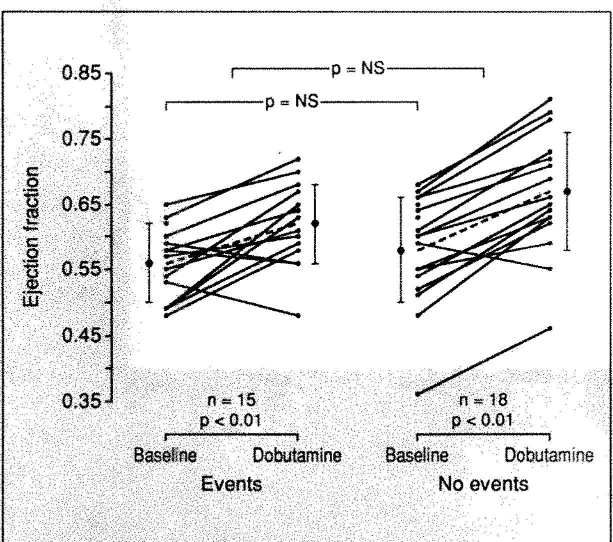


FIGURE 3. Individual, mean ± SD data for echocardiographic ejection fraction measured at baseline (n = 33) and peak stress (n = 30) for patients with and without cardiac events during follow-up. Significance values within and between groups are also shown.

Both all (n = 23) and hard (n = 10) cardiac events during follow-up occurred significantly more often in patients with a positive stress echocardiogram (Figure 2). Transient regional asynergy was inducible in 17 of 23 patients (74%) with and in 8 of 28 patients (29%) without events ($p < 0.01$); 5 of 6 patients (83%) with involvement of 3 segments had events. Myocardial infarction or unstable angina occurred in 8 of 25 (32%) with a positive and 2 of 26 (8%) with a negative dobutamine echocardiogram ($p < 0.05$; Figure 2). Ejection fraction response was not helpful in predicting the presence or absence of 3-vessel disease, inducible regional asynergy or cardiac events (all p = NS) (Figure 3). The respective numbers of patients with normal coronary arteries, minor lesions or 1-, 2- or 3-vessel disease was 1, 0, 6, 7 and 11 in patients with a positive and 7, 6, 6, 4 and 3 in those with a negative stress echocardiogram ($p < 0.01$). Although a positive dobutamine electrocardiogram alone was not predictive of subsequent events (Table II), patients with both a positive dobutamine echocardiogram and electrocardiogram were at higher risk than those with 2 negative tests ($p < 0.05$) (Table III). The sensitivity, specificity, positive and negative predic-

TABLE III Proportion of Patients with Cardiac Events During Follow-Up by Results of Dobutamine Echocardiography and Electrocardiography, and Exercise Electrocardiography

		Dobutamine Stress Echocardiogram			
		Positive		Negative	
		Dobutamine ECG		Dobutamine ECG	
		Positive	Negative	Positive	Negative
Exercise ECG	Positive	9/13*	6/8	2/4	2/6
	Negative	0/2	2/2	0/1	2/15
		9/15†	8/10	2/5	4/21

*$p < 0.01$ versus group with 3 negative stress tests.
†$p < 0.05$ versus group with negative dobutamine echocardiogram and electrocardiogram.
ECG = electrocardiogram.

tive value and overall accuracy for predicting events was 74, 71, 68, 77 and 72% for dobutamine echocardiography and 48, 68, 55, 61 and 59% for dobutamine electrocardiography.

Exercise electrocardiography: During exercise, mean peak heart rate (140 ± 25 beats/min) and double product (23,266 ± 6,118 mm Hg/min) attained were similar in patients with and without events (Table II); 1 patient developed hypotension and remained event free. Exercise stress testing variables by event status and Kaplan-Meier curves for all and hard events by results of exercise electrocardiography are listed in Table II and Figure 4, respectively. Agreement between exercise electrocardiography and dobutamine echocardiography was 73%, and both exercise duration (389 ± 195 vs 517 ± 237 seconds, $p < 0.05$) and time to diagnostic ST-segment shift (291 ± 192 vs 447 ± 212 seconds, $p = 0.05$) were shorter in patients with inducible asynergy. The respective numbers of patients with normal coronary arteries, minor lesions or 1-, 2- or 3-vessel disease were 2, 2, 6, 9 and 12 in patients with a positive and 6, 4, 6, 2 and 2 in those with a negative exercise test ($p < 0.01$). The sensitivity (83%), specificity (57%), positive (61%) and negative (80%) predictive value and overall accuracy (69%) of exercise electrocardiography for predicting cardiac events was similar to those of dobutamine echocardiography (all p = NS). In patients with hard events (n = 10) a positive exercise test, dobutamine echocardiogram or dobutamine electrocardiogram was seen in 9, 8 and 7 instances, respectively. Patients with 3 positive stress tests had more events during follow-up than those with 3 negative tests ($p < 0.01$) (Table III).

DISCUSSION

Risk stratification of patients with known or suspected CAD is a major goal of noninvasive stress testing and significantly influences subsequent management.[1] The main determinants of an adverse prognosis include the presence of globally impaired left ventricular systolic function, ventricular arrhythmias and anatomically and functionally severe underlying CAD.[2,17,18] We excluded patients with an ejection fraction <30% or previously documented electrical instability because of lack of data on the safety of dobutamine stress testing in such situations. Since inducible regional asynergy on dobutamine echocardiography represents an accurate diagnostic end point for CAD[9,10] and implies jeopardized myocardium supplied by important flow-limiting coronary atheroma, this test may give useful prognostic information. These considerations prompted this study.

Numerous studies using exercise or pharmacologic stress combined with electrocardiography,[2,19] thallium scintigraphy[18,20] or radionuclide ventriculography[21] have confirmed that evidence of inducible myocardial ischemia predicts future cardiac events in patients with CAD. Reports assessing the prognostic value of stress echocardiography have also been encouraging.[6–8,22–24] Picano et al[23] identified a positive low-dose dipyridamole echocardiogram as the most powerful predictor of subsequent cardiac events in 539 patients with CAD followed up for a mean of 3 years. Ryan et al[6] found that treadmill exercise echocardiography was superior to standard exercise testing for risk stratification after myocardial infarction but only used 3 electrocardiographic leads and emphasized the problem of rapid recovery of wall motion abnormalities with postexercise image acquisition.

Dobutamine is a predominant β_1-receptor agonist and induces myocardial ischemia in patients with CAD by increasing left ventricular contractility, heart rate, wall stress and, therefore, myocardial oxygen demand beyond that which can be met by supply.[25] Like other investigators, we found it to be a safe and well-tolerated stress.[9,10,26] The relative predictive abilities of exercise electrocardiography and dobutamine echocardiography may represent a trade-off between the higher heart rates and double products attainable with exercise on the one hand (both $p < 0.01$) and the apparent superiority of wall motion over ST-segment analysis on the other.[3,4,9] To maximize the stress achieved with dobutamine we used a relatively long infusion regimen[27] after complete washout of antianginal treatment.

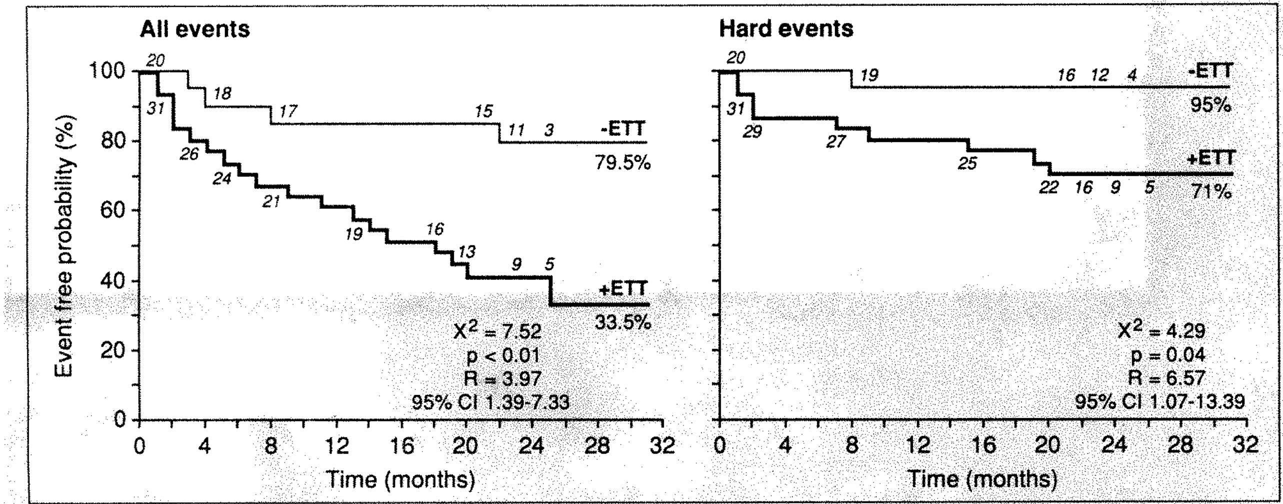


FIGURE 4. Kaplan-Meier curves for all *(left)* and hard *(right)* cardiac events during follow-up by results of exercise electrocardiography (+ETT or −ETT). Each *plot* represents the cumulative proportion of patients remaining event free. *Numbers* on the *graphs* indicate the total number of patients remaining at risk. CI = confidence interval; R = hazard ratio.

Several methodologic issues deserve comment. Although the probability analysis tables consulted[11] may not be strictly applicable to European populations, the estimates obtained agreed well with subsequent coronary angiography in that 43 of 51 patients (85%) had CAD. Because the stress echocardiographic findings were not routinely made available to managing clinicians, only the results of exercise electrocardiography could have led to post-test treatment bias by influencing the decision to recommend revascularization. Classification of coronary revascularization as a cardiac event is controversial because it depends on local availability of expertise, favorable anatomy and individual physician preference, but it likely also reflects the presence of severe symptoms or underlying CAD, or both. A separate analysis for hard events confirmed the predictive value of both dobutamine echocardiography and exercise electrocardiography (Figures 2 and 4).

Stress echocardiography and electrocardiography: Transient regional asynergy with dobutamine echocardiography was predictive of both total and hard cardiac events (Figure 2), and 5 of 6 patients with involvement of 3 segments had events. Exercise testing and coronary angiographic correlates indicate that dobutamine echocardiography identifies patients with extensive CAD, compromised coronary reserve and myocardial jeopardy, which likely explains its prognostic use, a contention supported by the significantly shorter exercise duration and time to diagnostic ST-segment shift in those with inducible asynergy. However, ejection fraction response to dobutamine was nondiscriminatory, perhaps reflecting variable reductions in afterload between patients, compensatory exaggerated hyperkinesia of normal wall segments, or the induction of new or worsening mitral regurgitation during the infusion[28] (Figure 3). Similarly negative conclusions have been reached by other workers.[6,29]

Both total and hard-event free survival were reduced in patients with a positive treadmill electrocardiogram, and exercise duration was significantly shorter in those who had events (Figure 4, Table II). These findings agree with data from the Coronary Artery Surgery Study registry on 4,083 patients with medically treated CAD in which the most prognostically useful exercise test variables were found to be exercise duration and ST-segment response.[2] Furthermore, registry data on patients with 3-vessel disease, preserved left ventricular function and diagnostic ST-segment deviation or low-exercise capacity showed that such patients had better 7-year survival if managed surgically rather than medically.[30]

Study limitations: Although wall motion analysis remains subjective, the good interrater agreement obtained in this (Figure 1) and from other reports[23] attests to the excellence of the eye as an integrator of space, time and motion. The relatively small number of events in this study did not permit a Cox regression model analysis.[15] Furthermore, the findings cannot necessarily be generalized to other groups such as patients who have had infarction, those requiring preoperative risk assessment, women or asymptomatic subjects. Therefore, these data need independent confirmation in larger and preferably multicenter studies also involving other patient groups with longer follow-up and more hard end points including mortality. Patients selected for prognostic studies are usually at low rather than intermediate risk, which affects the event rate and probably renders multiple noninvasive tests superior to any single test for risk stratification[19] (Table III). An additional limitation of stress testing for prognosis is that unpredictable events such as plaque rupture are not necessarily related to the presence of functionally significant CAD.

Clinical implications: Assuming equal efficacy, the choice of stress test for risk stratification depends on availability, cost and the level of local expertise. In addition to enabling accurate assessment of baseline global and regional left ventricular systolic function, dobutamine echocardiography can identify patients with severe flow-limiting CAD who are at increased risk of an adverse outcome. Dobutamine echocardiography may therefore aid selection for coronary angiography and prognostic revascularization, and is particularly suitable for patients with an equivocal or uninterpretable exercise electrocardiogram or those unable or poorly motivated to undertake exercise. With additional experience it may prove to be a useful alternative or addition to exercise testing in patients with CAD.

Acknowledgment: We are grateful to the Coronary Artery Disease Research Association and Eli Lilly for financial support. We also thank Senka Dinarevic, Mohammed Khan and Jayshree Joshi for technical help, Peter Clark for statistical advice, and Louise Perks for expert preparation of the illustrations.

REFERENCES

1. Chaitman BR. The changing role of the exercise electrocardiogram as a diagnostic and prognostic test for chronic ischemic heart disease. *J Am Coll Cardiol* 1986;8:1195–1210.

2. Weiner DA, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Ferguson JC, Fisher LD, Tristani F. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. *J Am Coll Cardiol* 1984;3:772–779.

3. Battler A, Froelicher VF, Gallagher KP, Scott Kemper W, Ross J. Dissociation between regional myocardial dysfunction and ECG changes during ischemia in the conscious dog. *Circulation* 1980;62:735–744.

4. Sugishita Y, Koseki S, Matsuda M, Tamura T, Yamaguchi I, Ito I. Dissociation between regional myocardial dysfunction and ECG changes during myocardial ischemia induced by exercise in patients with angina pectoris. *Am Heart J* 1983;106:1–7.

5. Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during stress in patients with syndrome X. *J Am Coll Cardiol* 1991;18:1463–1470.

6. Ryan T, Armstrong WF, O'Donnell JA, Feigenbaum H. Risk stratification after acute myocardial infarction by means of exercise two-dimensional echocardiography. *Am Heart J* 1987;114:1305–1316.

7. Jaarsma W, Visser CA, Funke Kupper AJ, Res JCJ, Van Eenige MJ, Roos JP. Usefulness of two-dimensional exercise echocardiography shortly after myocardial infarction. *Am J Cardiol* 1986;57:86–90.

8. Applegate RJ, Dell'Italia LJ, Crawford MH. Usefulness of two-dimensional echocardiography during low-level exercise testing early after uncomplicated acute myocardial infarction. *Am J Cardiol* 1987;60:10–14.

9. Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Williams R, Fineberg NS, Armstrong WF, Feigenbaum H. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991;83:1605–1614.

10. Berthe C, Pierard LA, Hiernaux M, Trotteur G, Lempereur P, Carlier J, Kulbertus HE. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. *Am J Cardiol* 1986;58:1167–1172.

11. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;300:1350–1358.

12. Corday E, Hajduczki I, O'Byrne GT, Kar S, Areeda J, Corday SR. Echocardiographic criteria to distinguish reversible from irreversible myocardial ischemia. *Eur Heart J* 1988;9(suppl F):29–43.

13. Starling MR, Crawford MH, Sorensen SG, Levi B, Richards KL, O'Rourke RA. Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide angiography for estimating left ventricular size and performance. *Circulation* 1981;63:1075–1084.

14. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85:546–562.

15. Altman DG. Practical Statistics for Medical Research. 1st ed. London: Chapman and Hall, 1991:365–396.

16. Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. New York: John Wiley, 1981:212–236.

17. Mock MB, Ringqvist I, Fisher LD, Davis KB, Chaitman BR, Kouchoukos NT, Kaiser GC, Alderman E, Ryan TJ, Russell RO, Mullin S, Fray D, Killip T III, and participants in the Coronary Artery Surgery Study. Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1982;66:562–568.

18. Gibson RS, Watson DD, Craddock GB, Crampton RS, Kaiser DL, Denny MJ, Beller GA. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. *Circulation* 1983;68:321–336.

19. Candell-Riera J, Permanyer-Miralda G, Castell J, Rius-Davi A, Domingo E, Alvarez-Aunon E, Olona M, Rossello J, Ortega D, Domenech-Torne FM, Soler-Soler J. Uncomplicated first myocardial infarction: strategy for comprehensive prognostic studies. *J Am Coll Cardiol* 1991;18:1207–1219.

20. Leppo JA, O'Brien J, Rothendler JA, Getchell JD, Lee VW. Dipyridamole thallium-201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. *N Engl J Med* 1984;310:1014–1018.

21. Miller TD, Taliercio CP, Zinsmeister AR, Gibbons RJ. Risk stratification of single or double vessel coronary artery disease and impaired left ventricular function using exercise radionuclide angiography. *Am J Cardiol* 1990;65:1317–1321.

22. Sawada SG, Ryan T, Conley MJ, Corya BC, Feigenbaum H, Armstrong WF. Prognostic value of a normal exercise echocardiogram. *Am Heart J* 1990;120:49–55.

23. Picano E, Severi S, Michelassi C, Lattanzi F, Masini M, Orsini E, Distante A, L'Abbate A. Prognostic importance of dipyridamole-echocardiography test in coronary artery disease. *Circulation* 1989;80:450–457.

24. Iliceto S, Caiati C, Ricci A, Amico A, D'Ambrosio G, Ferri GM, Izzi M, Lagioia R, Rizzon P. Prediction of cardiac events after uncomplicated myocardial infarction by cross-sectional echocardiography during transesophageal atrial pacing. *Int J Cardiol* 1990;28:95–103.

25. Meyer SL, Curry GC, Donsky MS, Twieg DB, Parkey RW, Willerson JT. Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease. *Am J Cardiol* 1976;38:103–108.

26. Mannering D, Cripps T, Leech G, Mehta N, Valantine H, Gilmour S, Bennett ED. The dobutamine stress test as an alternative to exercise testing after acute myocardial infarction. *Br Heart J* 1988;59:521–526.

27. Leier CV, Unverferth DV. Dobutamine. *Ann Intern Med* 1983;99:490–496.

28. Zachariah ZP, Hsiung MC, Nanda NC, Kan MN, Gatewood RP. Color Doppler assessment of mitral regurgitation induced by supine exercise in patients with coronary artery disease. *Am J Cardiol* 1987;59:1266–1270.

29. Freeman ML, Palac R, Mason J, Barnes WE, Eastman G, Virupannavar S, Loeb HS, Kaplan E. A comparison of dobutamine infusion and supine bicycle exercise for radionuclide cardiac stress testing. *Clin Nucl Med* 1984;9:251–255.

30. Weiner DA, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Fisher LD, Tristani F. Value of exercise testing in determining the risk classification and the response to coronary artery bypass grafting in three vessel coronary artery disease: a report from the Coronary Artery Surgery Study (CASS) registry. *Am J Cardiol* 1987;60:262–266.

Prognostic Value of Noninvasive Cardiac Tests in the Assessment of Patients with Peripheral Vascular Disease

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Two hundred thirty-six patients with peripheral vascular disease were prospectively studied to assess whether noninvasive cardiac investigations could predict prognosis better than simple clinical assessment. Clinical history, examination and resting electrocardiography were considered in all patients; exercise electrocardiography, Holter monitoring, radionuclide ventriculography and dipyridamole thallium imaging were performed in a subgroup of 168 patients. Follow-up for 6 to 30 months revealed major cardiac events in 21 patients. Cox survival analysis showed that clinical evidence of prior coronary artery disease was the best variable from clinical assessment that predicted cardiac events, with no other clinical variable adding to the statistical model. When variables from noninvasive cardiac assessment were added to the model, which included clinical evidence of coronary artery disease, dipyridamole thallium heart:lung ratio and left ventricular ejection fraction added significantly and incrementally to the prediction of cardiac events. Results of exercise electrocardiography or Holter monitoring did not add significantly. It is concluded that high lung uptake of thallium during dipyridamole stress, and impaired left ventricular ejection fraction help to identify patients with peripheral vascular disease who are at high cardiac risk, and should therefore be used for selecting subsequent cardiovascular medical, surgical and anesthetic management.

(Am J Cardiol 1993;71:40-44)

Patients with peripheral vascular disease (PVD) have a mortality 2 to 4 times that expected,[1,2] and more than half of the deaths are due to the almost ubiquitous coronary atheroma present in these patients.[3] Younger patients are at higher relative risk,[4] and there is a particularly high risk in the perioperative period.[5] Patients with prior clinical manifestations of coronary artery disease (CAD) are at higher risk in both the perioperative period[6] and the long term.[6,7] Perioperative risk is higher in patients with reversible myocardial ischemia[8,9] or poor left ventricular function[10] on preoperative noninvasive testing. Most patients with PVD do not undergo vascular surgery. The incremental value of noninvasive cardiac studies for the prediction of cardiac events or death compared with that of simple, readily obtained, clinical information has not been assessed. We prospectively assessed the incremental value of a number of common, noninvasive cardiac tests in identifying the risk of cardiac events in the long term in a typical, mixed population of patients with PVD.

METHODS

We investigated 145 patients prospectively with intermittent claudication, who were not scheduled for peripheral vascular surgery, from the vascular clinic of a district general hospital. Patients who already had arteriographically proved CAD were excluded from the study. We also studied 91 consecutive patients in whom elective surgery for abdominal aortic aneurysm, occlusive PVD or carotid arterial disease was scheduled.

There was no formal age limit, but patients with other serious illness (severe chronic obstructive airways disease, stroke, cancer or dementia) were excluded, as were those previously found to be unsuitable for vascular surgery owing to coexisting disease or age.

All patients gave informed consent, and the study was approved by the Northwick Park Hospital Ethical Committee.

Clinical assessment: Clinical assessment, resting electrocardiography, and fasting blood samples produced 18 variables for subsequent analysis (Table I). Clinical evidence of CAD was defined by prior myocardial infarction and history of angina or congestive heart failure. Left ventricular hypertrophy was defined by Romhilt and Estes'[11] electrocardiographic criteria.

Noninvasive cardiac assessment: Of 145 patients not scheduled for peripheral vascular surgery, 16 underwent elective investigation at the request of the vascu-

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lar surgeon; of the remaining 129, 61 were randomized to undergo noninvasive studies and 68 underwent no further investigation as part of a control group with a separate study. All 91 patients assessed before surgery underwent noninvasive cardiac tests; thus, in all, 168 underwent noninvasive cardiac assessment.

Standard methods were used for treadmill and ambulatory electrocardiographic assessment.[12] Patients with bundle branch block or left ventricular hypertrophy on their resting electrocardiogram and those receiving digoxin were not considered suitable for ST-segment trend analysis. Maximal exercise heart rate was recorded as a percentage of the maximal expected rate, and exercise time was noted. Exercise tests were defined as positive at 1 mm ST-segment depression at J + 60 ms. Likewise, on ambulatory electrocardiographic monitoring, episodes of ST depression >1 mm and lasting ≥1 minute were recorded as ischemic.

Standard techniques using in vivo labeling of red cells with technetium-99m were used for resting radionuclide ventriculography. Left ventricular ejection fraction was calculated semiautomatically.[13]

Dipyridamole thallium-201 imaging was performed using standard techniques.[14] Oral dipyridamole and theophylline preparations were discontinued in patients who were receiving regular treatment; other medications were taken as usual. Intravenous dipyridamole (0.56 mg/kg over 4 minutes) was followed by low-level bicycle exercise for 3 minutes, which is thought to improve image quality and reduce vasodilatory side effects.[15] Planar and tomographic images were acquired after stress and 4 hours later. Regions of interest were positioned over areas of maximal myocardial and lung uptake of thallium-201 on the anterior planar images, and the heart:lung thallium-201 ratio was calculated.[16] Tomographic myocardial images were categorized in regard to whether they were normal, or had reversible defects representing ischemia or fixed defects representing myocardial infarction.[17]

Cardiac catheterization: Mainly on the basis of abnormal thallium-201 imaging and cardiac symptoms, 54 patients underwent cardiac catheterization and revascularization, as appropriate.

Follow-up: The subsequent surgical and cardiac progress of patients were documented from hospital visits, telephone interviews of patients or their family doctor, or both, and from the Office of Population Censuses and Surveys. Major cardiac events were defined as death due to myocardial infarction, heart failure or sudden death, plus nonfatal myocardial infarction, unstable angina or coronary artery bypass surgery. Follow-up ranged between 9 and 30 months.

Cox survival analysis: Initially, 18 clinical variables (Table I) were considered for inclusion in a statistical model to predict event-free survival. A second set of 8 variables, derived from the noninvasive cardiac investigations, included exercise time, percent maximal predicted heart rate, exercise and ambulatory ischemia, left ventricular ejection fraction, heart:lung thallium-201 ratio, reversible thallium-201 defect, and fixed or reversible (or both) thallium-201 defect. These variables were added 1 at a time to find which (if any) would improve the statistical model predicting event-free survival. This approach was used to find whether noninvasive cardiac investigations could add significantly and incrementally to the prediction of patients more likely to have an event. Relative risks of events and estimated survival function curves were generated from the survival analysis.

TABLE I Overall Features of Study Population (n = 236)

Age (year)	68.5 ± 8.6
Men	91 (71%)
Scheduled for operation	59 (39%)
Presence of aortic aneurysm	59 (25%)
Mean ankle:brachial blood pressure ratio	0.82 ± 0.18
Continued smoking at time of assessment	97 (41%)
Hypertension on history or examination	119 (50%)
Diabetes mellitus on history or fasting blood sugar	28 (12%)
Previous myocardial infarction	61 (26%)
Clinical evidence of coronary artery disease	91 (39%)
Clinical evidence of cerebrovascular disease	27 (11%)
Plasma fibrinogen (mg%)	370 ± 85
Fasting total serum cholesterol (mM)	6.7 ± 1.4
Fasting serum triglycerides (mM)	1.7 ± 1.0
Erythrocyte sedimentation rate (mm/hr)	17 ± 14
Left ventricular hypertrophy on resting ECG	58 (25%)
Intention to treat with aspirin during follow-up	120 (51%)
Intention to treat with calcium antagonist	97 (41%)

ECG = electrocardiography.

TABLE II Results of Noninvasive Cardiac Investigations (n = 168)

Exercise ECG	Invalid 65 (41%) Normal 50 (31%) Ischemic 44 (28%) Exercise time 379 ± 242 s % max. predicted HR achieved 89 ± 18%
Ambulatory ECG	Invalid 68 (40%) Normal 74 (45%) Ischemic 21 (13%)
Radionuclide ventriculography	Mean EF 54.0 ± 13.3% (range 9 to 83)
Dipyridamole thallium-201 (n = 167)	Normal 50 (30%) Fixed defects only 32 (19%) Reversible defect 85 (50%) Mean heart:lung ratio 2.2 ± 0.6 (range 1.08 to 4.2)

ECG = electrocardiography; EF = ejection fraction; HR = heart rate.

RESULTS

The results of clinical assessment are summarized in Table I, and were as expected from other series.[3] Results of noninvasive cardiac tests are listed in Table II. Resting electrocardiographic changes precluded ST segment for analysis of ischemia in 41% of patients during exercise or ambulatory monitoring. Treadmill exercise was not possible for various reasons in 9 patients, and many other patients were limited by claudication, such that they could not achieve a heart rate sufficient for diagnostic purposes, as reflected by the mean percent maximal predicted heart rate achieved. Ambulatory monitoring failed for technical reasons in 5 patients.

Radionuclide ventriculography was technically successful in all patients, but the left ventricular ejection fraction derived should be cautiously interpreted in the 12% of patients with atrial fibrillation. Dipyridamole thallium-201 imaging was successful in all patients, except 1 who had an asthmatic attack; only 4% had significant side effects, which resolved uneventfully with intravenous aminophylline (125 to 250 mg), as expected. Fixed or reversible perfusion defects were observed in 70% of patients; in 54 of these who later underwent coronary arteriography, the positive predictive value of an abnormal thallium-201 image was 94%. The range of heart:lung thallium-201 ratio values reflected the widely differing lung uptake of thallium-201; high ratios correlated with small lung uptake, and low ratios correlated with marked lung uptake.

Follow-up: Follow-up was complete, except for the exact cause of death in 2 patients with aortic aneurysms who died suddenly outside hospital; whether these deaths were due to aneurysmal rupture or known CAD was not established. Cardiac events occurred in 21 of all 236 patients and in 18 of the 168 who had noninvasive cardiac investigations. Cardiac events included 4 deaths due to congestive heart failure, 2 sudden cardiac deaths, 1 death due to myocardial infarction, 5 nonfatal infarctions, 3 episodes of unstable angina (2 of which eventually progressed to infarction), and 6 coronary artery bypass grafts (3 before scheduled surgery for PVD).

Cox survival analysis: When clinical variables were compared with subsequent cardiac events, clinical evidence of CAD was found to be the best predictor of cardiac events (global chi-square 8.1), and no other variable added significantly to it. When the results of noninvasive cardiac investigations were added individually to clinical evidence of CAD, only heart:lung thallium-201 ratio and left ventricular ejection fraction significantly improved the prediction of cardiac events (global chi-square 17.7 and 17.25, respectively).

In the first statistical model, the relative risks of a subsequent cardiac event in patients with prior clinical evidence of CAD was 4.7 (range 1.6 to 13.6) compared with those with no CAD; patients with increased lung

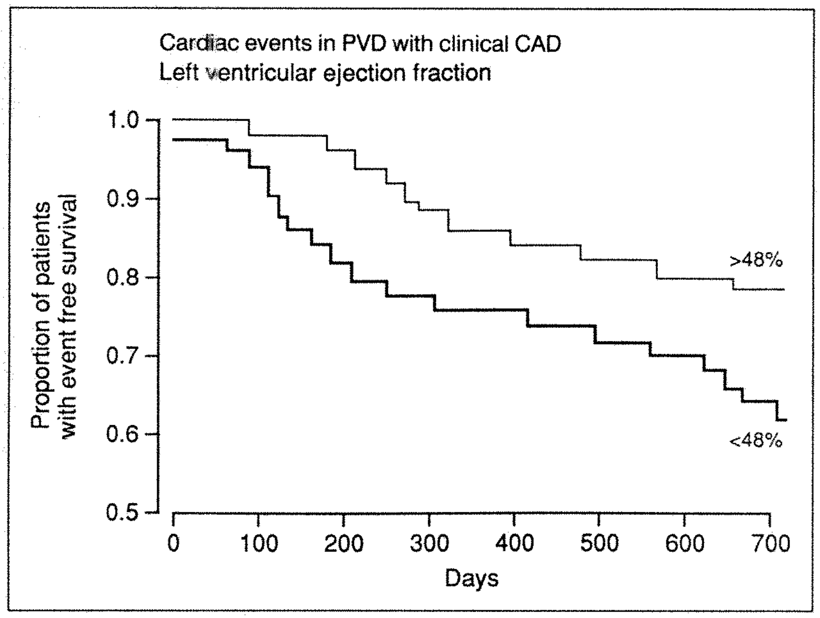

FIGURE 1. Estimated survival function curves generated from Cox survival analysis. This shows different survival curves of patients with prior clinical evidence of coronary artery disease (CAD) with left ventricular ejection fraction > or < our laboratory's lower limit of normal (48%). PVD = peripheral vascular disease.

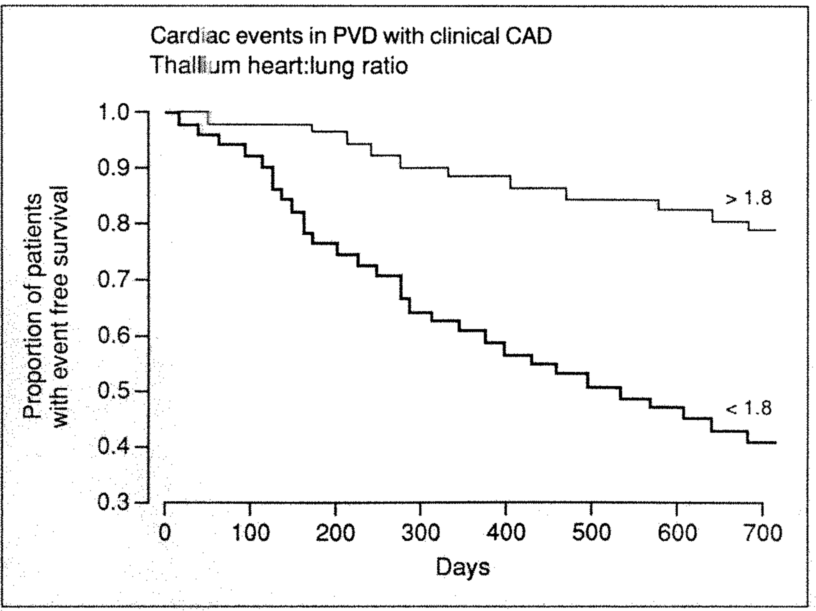

FIGURE 2. Estimated survival funtion curves generated from Cox survival analysis. This shows different survival curves of patients with prior clinical evidence of coronary artery disease (CAD) with a heart:lung thallium ratio > or <1.8. PVD = peripheral vascular disease.

uptake of thallium-201 (i.e., those with a heart:lung ratio 0.5 lower than the mean value of 2.2) had an additional relative risk of 1.8 (1.1 to 3.1). In the second model, the relative risk with prior clinical evidence of CAD was 3.7 (1.2 to 11.4); patients with a left ventricular ejection fraction that was 20% less had an additional relative risk of 1.9 (1.0 to 3.6).

Figures 1 and 2 show estimated survival function curves generated from Cox survival analysis; cardiac event-free survival is compared in patients with clinical evidence of CAD who have low or high lung uptake of thallium-201 and in those with high or low left ventricular ejection fraction.

DISCUSSION

Our findings reinforce the results of previous studies that found that clinical evidence of CAD is an important predictor of patients likely to have a cardiac event.[3,5,18,19] The relative risk of a major cardiac event during follow-up was 4 times greater in patients with simple clinical evidence of prior CAD. However, this study extends across the entire spectrum of patients with PVD, not just those undergoing preoperative or postoperative assessment. No patient had the traditional clinical indicators of high cardiac risk, such as recent myocardial infarction or unstable angina, and only a few had overt cardiac failure; those at high relative risk had a prior myocardial infarction or stable angina.

An important finding of this study that was not described previously is that increased lung uptake of thallium-201 during dipyridamole stress is associated with a worse prognosis. The prognostic importance of lung uptake during exercise stress has been described several times[20,21]; it is thought to represent exercise-induced impairment of left ventricular function with elevation of pulmonary venous pressure and transient pulmonary edema.[22] Lung uptake of thallium-201 during dipyridamole stress was previously shown to be higher in patients with CAD than in those without.[23]

As in previous studies, evidence of impaired left ventricular ejection fraction predicted patients more likely to die during follow-up.[24] In the survival analysis, this did not add significantly to the Cox model, if the thallium-201 heart:lung ratio was already included and vice versa; this suggests that they both provide similar information for survival analysis (i.e., poor left ventricular function).

It is of clinical importance that these noninvasive cardiac studies were able to add incrementally to the prediction of patients at high cardiac risk. Lung uptake of thallium-201 was the most important variable to add, followed by left ventricular ejection fraction. It may be possible to recommend dipyridamole thallium-201 imaging as the method of choice, because resting electrocardiographic changes and rhythm abnormalities do not preclude patients from this study, and it not only provides prognostic information and ventricular function information from the heart:lung ratio, but also information regarding regional myocardial perfusion and potential benefit from revascularization.

No other noninvasive cardiac variables, in particular those from ambulatory electrocardiographic monitoring and reversible ischemia on thallium-201 imaging, added incremental prognostic information to clinical evidence of CAD in contrast to the results of other series.[8,9,25,26] Probable explanations for this include the following: Electrocardiographic analysis for ischemia was prevented in 40% of cases by resting electrocardiographic changes, limiting both ambulatory and exercise analysis; exercise tolerance was largely limited by claudication that would limit cardiac ischemia and remove the prognostic value of exercise time or maximal heart rate; and discovery of reversible ischemia on thallium-201 imaging may have led to aggressive medical management of patients, because clinicians could not be blinded to the results of noninvasive cardiac studies. Differences in methodology may also contribute to differences between studies, including the inclusion of patients not undergoing surgery in our series, different intensities of perioperative and long-term surveillance for cardiac events, varying definitions of cardiac events, and inclusion of clinical evidence of CAD in the Cox survival analysis before assessing the contribution of noninvasive cardiac studies.

There are some limitations to this study. It was relatively small and had a limited follow-up; however, for a Cox survival analysis model, there should be approximately 10 times as many events as covariates, so that the study was sufficiently large to find 2 covariates that predict outcome. The advantage of a smaller study is that it can be performed in 1 center. There was also a mixture of patients with different types and severities of PVD. However, all types of patients with PVD are at high risk of cardiac events, and when these variables (presence of aortic aneurysm and mean ankle:brachial blood pressure ratio) were entered in the survival analysis, they did not add to the prediction of outcome. Finally, heart:lung ratio and ejection fraction are quantitative variables that have an advantage in a survival analysis when compared with categoric variables, such as the presence of ST-segment changes on ambulatory or exercise electrocardiographic monitoring.

In summary, we have shown that clincal evidence of previous CAD is the most important predictor of patients at risk of a subsequent cardiac event, and further incremental information can be obtained from patients' left ventricular function by analysis of lung uptake of thallium-201 during dipyridamole stress or from their left ventricular ejection fraction. This should have an important role in helping to decide patients' subsequent medical, anesthetic and surgical management, and may also direct subsequent research trials of interventions toward those at high risk.

REFERENCES

1. Dormandy J and the Members of the Steering and Executive Committees of the Multi-National Study on the Prevention of Atherosclerotic Complications by Ketanserin (PACK). Fate of the patient with chronic leg ischaemia. *J Cardiovasc Surg* 1989;30:50–57.

2. Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors and mortality. The Whitehall Study. *Circulation* 1990;82:1925–1931.

3. Hertzer NR, Beven EG, Young, O'Hara PJ, Ruschhaupt WJ, Graor RA, Dewolfe WF, Maljovec LC. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984;199:223–233.

4. Reigel MM, Hollier LH, Kazmier FJ, O'Brien PC, Pairolero PC, Cherry KJ, Hallett JW. Late survival in abdominal aortic aneurysm patients: the role of selective myocardial revascularization on the basis of clinical symptoms. *J Vasc Surg* 1987;5:222–227.

5. Crawford ES, Bomberger RA, Glaeser DH, Saleh SA, Russell WI. Aortoiliac occlusive disease; factors influencing survival and graft function following reconstructive operation over 25 years. *Surgery* 1981;90:1055–1067.

6. Hall R, Coupland G, Lane R, Appleberg M. Abdominal aortic aneurysms and coronary artery disease: is a more aggressive approach indicated? *Aust N Z J Surg* 1987;57:311–315.

7. Begg TB, Richards RL. The prognosis of intermittent claudication. *Scott Med J* 1962;7:341–352.

8. Eagle KA, Singer DE, Brewster DC, Darling RC, Mulley AG, Boucher CA. Dipyridamole-thallium scanning in patients undergoing vascular surgery. *JAMA* 1987;257:2185–2189.

9. Raby KE, Goldman L, Creager MA, Cook EF, Weisberg MC, Whittmore AD, Selwyn AP. Correlation between preoperative ischaemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989;321:1296–1300.

10. Pastemak PF, Imparato AM, Bear G, Riles TS, Baumann FG, Benjamin D, Sanger J, Kramer E, Wood RP. The value of radionuclide angiography as predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm resection. *J Vasc Surg* 1984;1:320–325.

11. Romhilt DW, Estes EH. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J* 1968;75:752–758.

12. Subramanian B, Bowles M, Lahiri A, Davies AB, Raftery EB. longterm antianginal action of verapamil assessed with quantitated serial treadmill stress testing. *Am J Cardiol* 1981;48:529–535.

13. Hains AGB, Al-Khawaja I, Hinge DA, Lahiri A, Raftery EB. Radionuclide left ventricular ejection fraction: a comparison of three methods. *Br Heart J* 1987;57:242–246.

14. Leppo JA. Dipyridamole-thallium-201 imaging: the lazy man's stress test. *J Nucl Med* 1989;30:281–287.

15. Casale PN, Guiney TE, Strauss W, Boucher CA. Simultaneous low level treadmill exercise and intravenous dipyridamole stress thallium-201 imaging. *Am J Cardiol* 1988;61:799–802.

16. Al-Khawaja, Lahiri A, Rodrigues EA, Heber ME, Raftery EB. Clinical significance of exercise-induced pulmonary uptake of thallium in uncomplicated myocardial infarction. *Am J Card Imag* 1988;2:135–141.

17. Pohost GH, Zir LM, Moore RH, McKusick KA, Guiney TE, Beller GA. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 1977;55:294–302.

18. De Bakey ME, Crawford ES, Cooley DA, Morris GC, Royster TS, Abbott WP. Aneurysm of abdominal aorta. Analysis of results of graft replacement therapy one to eleven years after operation. *Ann Surg* 1964;160:622–639.

19. Hollier LH, Plate G, O'Brien PC, Kazimer FJ, Gloviczki P, Pairolero PC, Cherry KJ. Late survival after abdominal aortic aneurysm repair: influence of coronary artery disease. *J Vasc Surg* 1984;1:290–129.

20. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium-201 uptake by the lungs during exercise in coronary artery disease. *N Engl J Med* 1987;17:1485–1489.

21. Kaul S, Finkelstein DM, Homma S, Leavitt M, Okada RD, Boucher CA. Superiority of quantitative exercise thallium-201 variables in determining long term prognosis in ambulatory patients chest pain: a comparison with cardiac catheterization. *J Am Coll Cardiol* 1988;12:25–34.

22. Lahiri A, O'Hara M, Bowles MJ, Crawley JCW, Raftery EB. Influence of left ventricular function and severity of coronary artery disease on exercise- induced pulmonary thallium-201 uptake. *Int J Cardiol* 1984;5:475–490.

23. Okada RD, Dai Yu-Hua, Boucher CA, Pohost EM. Significance of increased lung thallium-201 activity on serial cardiac images after dipyridamole treatment in coronary heart disease. *Am J Cardiol* 1984;53:470–475.

24. Killip T, Passamani E, Davis K, and the CASS principal investigators and their associates. Coronary artery surgery study (CASS): a randomized trial of coronary bypass surgery. *Circulation* 1985;72(suppl V):102–109.

25. McPhail N, Menkins A, Shariatmadar A, Calvin J, Barber G, Scobie K, White P. Statistical prediction of cardiac risk in patients who undergo vascular surgery. *Can J Surg* 1985;28:404–406.

26. Von Knorring J, Lepantalo M. Prediction of peri-operative cardiac complications by ECG monitoring during treadmill exercise testing before peripheral vascular surgery. *Surgery* 1986;99:610–613.

Rationale and Design of the Department of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (HIT) for Secondary Prevention of Coronary Artery Disease in Men with Low High-Density Lipoprotein Cholesterol and Desirable Low-Density Lipoprotein Cholesterol

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Although a large body of epidemiologic evidence suggests that low levels of high-density lipoprotein (HDL) cholesterol are strongly associated with an increased risk of coronary artery disease (CAD), no large-scale clinical trials focusing on this association have been reported. This report describes the rationale and design of the Department of Veterans Affairs HDL Intervention Trial (HIT), a multicenter, randomized, controlled clinical trial designed to determine whether lipid therapy reduces the combined incidence of CAD death and nonfatal myocardial infarction in men with established CAD who have low levels of HDL cholesterol with "desirable" levels of low-density lipoprotein (LDL) cholesterol. Twenty-five hundred men with CAD and HDL cholesterol ≤40 mg/dl, LDL cholesterol ≤140 mg/dl, and triglycerides ≤300 mg/dl are being recruited at 20 Department of Veterans Affairs medical centers, randomized to either gemfibrozil or placebo, and followed in a double-blind manner for an average of 6 years. In this population, gemfibrozil is expected to increase HDL cholesterol by 10 to 15%, have a negligible effect on LDL cholesterol, and lower triglycerides by 30 to 40%. Because an estimated 20 to 30% of patients with CAD have a low HDL cholesterol as their primary lipid abnormality, the results of this trial are expected to have far-reaching clinical implications.

(Am J Cardiol 1993;71:45–52)

Despite a wealth of epidemiologic data suggesting that low levels of high-density lipoprotein (HDL) cholesterol are strongly associated with increased risk for coronary artery disease (CAD), no reported clinical trials have specifically focused on this association and none have targeted people whose primary lipid abnormality is a low HDL cholesterol. In the absence of such trials we do not know whether patients with low HDL cholesterol (but without hypercholesterolemia) would benefit from lipid therapy, nor can we conclusively establish a causal relation between HDL cholesterol and CAD.[1] The Department of Veterans Affairs HDL Intervention Trial (HIT) is a multicenter, randomized, controlled trial designed to address these 2 issues. Specifically, the hypothesis of the study is that treatment with the fibric acid derivative, gemfibrozil, will reduce the combined incidence of CAD death and nonfatal myocardial infarction in men with established CAD and low HDL cholesterol in association with "desirable" low-density lipoprotein (LDL) cholesterol.

Although death rates from CAD have been declining in recent years, this disease continues to exact an enormous toll in the United States and other industrialized countries in terms of disability, lost lives, and dollars spent. Approximately 7 million Americans have clinically evident CAD and each year 500,000 die from this disease[2]; ultimately >80% of affected patients succumb to complications of their CAD.[3] Preventing morbidity and delaying mortality in this large population is therefore an important public health priority. Low HDL cholesterol, even in the absence of hypercholesterolemia, is one of the strongest risk factors for recurrent CAD morbidity and mortality.[4,5] This lipid profile (low HDL cholesterol without hypercholesterolemia) is found in 20

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*See Appendix.

to 30% of patients with CAD,[6-10] or in more than one and a half million people in this country. Expert groups and consensus panels have acknowledged the importance of HDL cholesterol as a risk factor for CAD, but have been reluctant to make any firm treatment recommendations for normocholesterolemic patients with low HDL cholesterol in the absence of any relevant clinical trial data.[11,12] The HIT, which examines the effects of treatment in this unique population, is thus expected to have important and far-reaching clinical implications.

Background: EPIDEMIOLOGIC EVIDENCE: A relation between low plasma HDL cholesterol and CAD was first reported by Barr et al[13] in a case-control study of survivors of myocardial infarction published in 1951. Although this observation was confirmed in numerous subsequent case-control studies, it was >25 years before the first cohort studies demonstrated that low levels of HDL cholesterol were predictive of the development of CAD. In 1977 the Framingham Heart Study reported that the incidence of CAD was >8 times higher among persons with HDL cholesterol <35 mg/dl than among those whose HDL cholesterol was >65 mg/dl.[14] In that same year, the Tromso Heart Study reported that, in a cohort of 6,500 men, HDL cholesterol was more strongly associated with incident CAD than any of the 8 other variables studied.[15] More than a dozen cohort studies in various countries have subsequently examined this relation and all but 2 have found low HDL cholesterol to be a strong, independent predictor of CAD.[16] Several studies have found that a low level of HDL cholesterol is the single best predictor of CAD events.[17-19] The relation is independent of other risk factors such as total cholesterol, body mass index, smoking and hypertension and is apparent in both men and women, elderly and middle-aged people, and those with and without CAD at baseline.

No large intervention trials specifically designed to study subjects who have low levels of HDL cholesterol have been reported. Some of the trials of lipid-lowering therapy in hypercholesterolemic subjects, however, have suggested that raising HDL cholesterol is associated with a reduction in CAD events[20,21] or with an improvement in angiographic evidence of coronary atherosclerosis.[22,23] Most important among these is the Helsinki Heart Study, which enrolled healthy middle-aged men chosen because of a high level of non-HDL cholesterol (mean LDL cholesterol 189 mg/dl). Those randomized to active treatment (gemfibrozil) had a mean HDL cholesterol increase of 11%, a mean LDL cholesterol decline of 11%, and a 34% reduction in CAD end points compared with the placebo group.[20,24] Statistical analyses of these data indicated that the increase in HDL cholesterol was independently associated with the reduction in end points. The data from both observational and intervention studies suggest that each 1 mg/dl increase in HDL cholesterol is associated with a 3 to 4% decrease in coronary events.[25]

BIOLOGIC MECHANISMS: In 1968, Glomset[26] first proposed a role for HDL in the reverse transport of cholesterol from arterial wall to liver, thus providing an explanation for the association between low HDL cholesterol and increased risk of CAD. Since then, many studies, reviewed in detail elsewhere,[27,28] have begun to elucidate possible mechanisms by which HDL may protect against the development of atherosclerotic vascular disease. Notable experimental observations include the demonstration that HDL promotes the efflux of cholesterol from extrahepatic cells in culture,[29] that HDL infusions result in the regression of atherosclerosis in a live animal model,[30] and that atherosclerosis can be inhibited by increasing HDL production in transgenic mice.[31]

In humans, a low HDL cholesterol frequently occurs in association with high triglycerides. It is possible that the risk of CAD associated with low levels of HDL cholesterol is at least partially related to metabolic abnormalities seen in the hypertriglyceridemic state. These include the accumulation of potentially atherogenic triglyceride-rich remnant lipoproteins,[32] a relative increase in the concentration of small, dense LDL particles that may be more susceptible to oxidation and cellular uptake than larger LDL,[33] and a decrease in fibrinolytic activity and other alterations in the coagulation system leading to a procoagulant state.[34,35]

The epidemiologic and biologic evidence accumulated to date is substantial and is generally consistent with the hypothesis that HDL cholesterol is causally related to CAD.[12] To confirm this hypothesis, however, and to determine the appropriate therapeutic approach for those with low HDL cholesterol will require data from clinical trials.

Study population: The population eligible for the HIT includes men aged ≤73 years with documented CAD and HDL cholesterol ≤40 mg/dl, LDL cholesterol ≤140 mg/dl, and triglycerides ≤300 mg/dl who are able to take the medication safely and have no other conditions likely to result in death in the ensuing 5 years. Whereas non-veterans are not formally excluded from participation, eligibility regulations at most of the participating sites make it difficult to enroll such subjects.

EXCLUSION OF WOMEN: Women have been excluded from most major cardiovascular clinical trials for many reasons, including the erroneous perception that CAD is not a major health problem for women. Although CAD is less common during the premenopausal years, rates of CAD in postmenopausal women approximate those seen in men[36] and CAD is the leading cause of death in women.[37] The association between HDL cholesterol and CAD is present in both genders[38,39]; in several studies low HDL cholesterol is even more strongly associated with CAD risk in women than in men.[38] Low levels of HDL cholesterol are at least as prevalent among female as among male patients with CAD.[6] There are thus strong a priori reasons for including women in this trial.

The nature of the population served by the Department of Veterans Affairs medical centers, however, precludes inclusion of women in this study. Approximately 2% of patients seen in this system are women and half are premenopausal.[40] It was therefore estimated that about 1% of patients with CAD at the participating sites would be women. If women enrolled in the trial at the same rate as men, there would be only 25 women among the 2,500 participants. Because women may have different responses to intervention than men, it would not be appropriate to analyze both genders together. However, an analysis of only 25 patients could not possibly provide any meaningful information and might be misleading. Thus, since it was not feasible for this trial to enroll enough women, we decided to study men only, leaving it to future trials to address this question in women.

LIPID CRITERIA: Target lipid values for the study population (HDL cholesterol ≤ 40 mg/dl, LDL cholesterol ≤ 140 mg/dl, and triglycerides ≤ 300 mg/dl) reflect an attempt to obtain a population that truly has low HDL cholesterol as its major lipid abnormality while not unduly restricting the pool of potentially eligible subjects. The National Cholesterol Education Program defines high-risk values as HDL cholesterol ≤ 35 mg/dl, LDL cholesterol ≥ 130 mg/dl, and triglycerides ≥ 250 mg/dl[11]; we placed our target values slightly above these levels in order to enhance recruitment. With these criteria we expect that all patients in the trial will have a total cholesterol <240 mg/dl, the level used to define "high blood cholesterol."[11] Furthermore, all patients should have LDL cholesterol levels substantially below the level (currently 160 mg/dl) at which drug therapy is recommended for CAD patients.[11] If the recommended treatment threshold for LDL cholesterol is lowered during the course of the trial, the Data Monitoring Board will consider the implications for enrolled subjects and may recommend protocol changes (e.g., addition of bile-acid binding resin if LDL cholesterol exceeds a certain value).

To obtain a population whose lipid values at the time of randomization are at or below target levels, we developed a multistage lipid screening program. This program was designed to maximize the yield of subjects with the target lipid profile while minimizing the number of tests required. A computer simulation that incorporated lipid profiles from actual studies of men with CAD evaluated different screening rules. We took into account the effects of regression to the mean and the possibility that we had inaccurately specified the lipid distributions. The resulting lipid criteria for each stage of screening are listed in Table I. These screening rules will be evaluated during the early phase of the trial and modified if necessary.

OTHER ENTRANCE CRITERIA: Patients must have documented CAD (history of either myocardial infarction, coronary artery revascularization procedure, angiographic evidence of coronary atherosclerosis, or angina corroborated by objective evidence of ischemia) and no evidence of other life-threatening medical illness, alcohol or substance abuse, cholelithiasis, marked left ventricular dysfunction, or inability or unwillingness to take the medication and comply with follow-up visits. These entrance criteria permit enrollment of a heterogeneous sample, including the elderly, smokers, well-controlled diabetics, hypertensives, and patients who are obese, have mild left ventricular dysfunction, or are taking β blockers or thiazide diuretics.

The advantages to a heterogeneous population are that the results are more generalizable, the study sample is easier to assemble, and treatment effects can be examined in various subgroups. Subgroups of particular interest in this study have been specified in advance and are defined by the following: baseline lipids, β-blocker and aspirin use, smoking status, history of prior myocardial infarction, time since last myocardial infarction and/or other measures of the "activity" of CAD at baseline, left ventricular function, age, race, diabetes, hypertension and family history. Subgroup analyses are intended to help elucidate mechanisms and generate new hypotheses.

TABLE I Multistage Lipid Screen

	Eligibility Criteria (mg/dl)
Visit 1	
HDL cholesterol	≤ 42
LDL cholesterol	≤ 145
TG	≤ 350
Visit 2	
HDL cholesterol	(HDL1* and HDL2 ≤ 40) or (HDL2 ≤ 40 and mean† HDL ≤ 38)
LDL cholesterol	LDL2 ≤ 140 and mean† LDL ≤ 140
TG	(TG1 and TG2 ≤ 300) or (TG2 ≤ 300 and mean† TG ≤ 270)

*The digit 1 or 2 after HDL, LDL or TG refers to the value from visits 1 or 2, respectively.

†Mean of the values from visits 1 and 2.

Lipid profiles from visit 3 and the baseline visit are not used to determine eligibility; they are averaged to determine baseline lipid values. The mean total cholesterol from visits 1 and 2 must be > 100 mg/dl.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

Treatment regimen: The treatment regimen consists of 1,200 mg of extended-release gemfibrozil (Lopid SR™) or matching placebo given once daily. We considered the ideal intervention for this trial to be a safe, well-tolerated regimen that effectively raised HDL cholesterol without affecting other lipid parameters. Although weight loss is a safe and moderately effective way to raise HDL cholesterol,[41] it is notoriously difficult to achieve and maintain and is only applicable to those who are overweight. Bile-acid binding resins and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors were not considered suitable because of their limited ability to raise HDL cholesterol consistently and their substantial LDL cholesterol-reducing effect.[42] Although niacin is highly effective at raising HDL cholesterol, it also lowers LDL cholesterol significantly and is associated with frequent and troubling side effects,[42] which we anticipated would lead to high rates of noncompliance in our population as well as difficulty maintaining the blind. Furthermore, the many relative contraindications to niacin (e.g., diabetes, peptic ulcer disease and gout) would limit the eligible population.

We chose gemfibrozil because of its established safety and tolerability and its anticipated ability to raise HDL cholesterol consistently with minimal effects on LDL cholesterol. Based on limited data in normocholesterolemic subjects with low HDL cholesterol ([43] and Stettler et al, unpublished observations) we projected that gemfibrozil would raise HDL cholesterol by 10 to 15%, lower triglycerides by 30 to 40% and total cholesterol by 10 to 15%, and have a negligible effect on LDL cholesterol.

Recruitment and screening (Figure 1): The trial began screening patients on August 1, 1991. Several recruitment strategies are being used, including direct mail with telephone follow-up of patients with probable CAD who have been identified from various sources (e.g., pharmacy computer printouts listing patients on nitrates, direct patient solicitation in cardiology and general medicine clinics, physician referral, and advertising in the hospital and to veterans' groups and the general community). Men aged ≤73 years with known CAD are invited to attend the first screening visit.

At the first screening visit, patients are given a brief questionnaire to determine eligibility and, if no exclusions are identified, a lipid profile is obtained. Patients whose first profile meets criteria are invited for a second lipid profile and laboratory screen (complete blood count, liver and kidney function tests, glucose, urinalysis). Those who remain eligible are invited to a final screening visit during which the study is explained in detail and written informed consent is obtained. A history and physical examination, detailed chart review, and lipid profile are performed and, if indicated by algorithm (Figure 2), a radionuclide ventriculogram is also recorded at this visit.

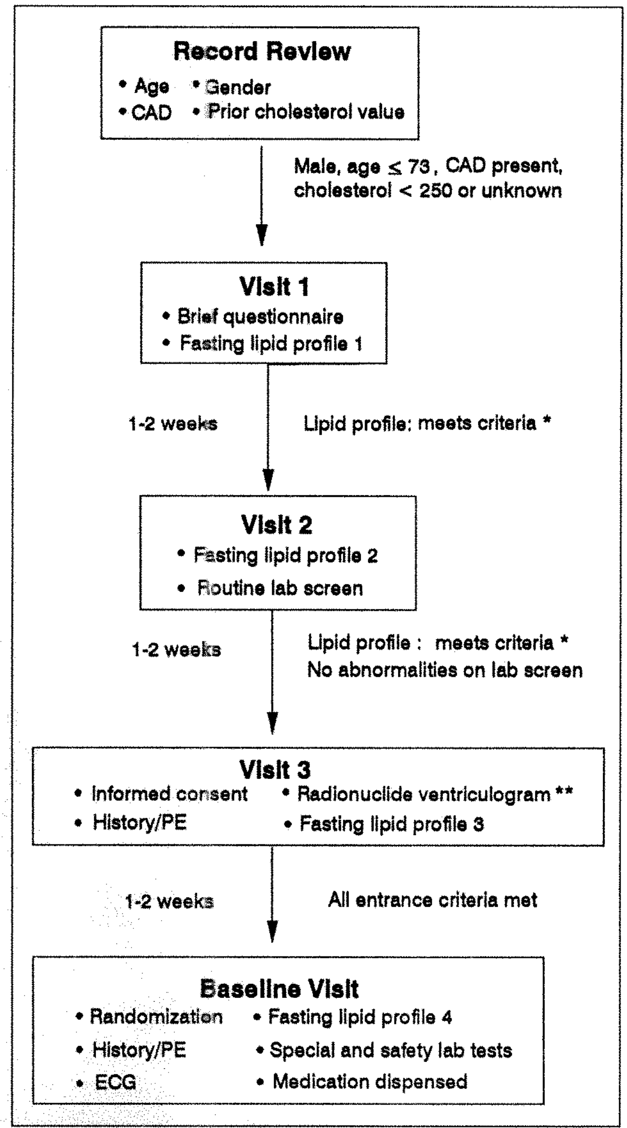
Record Review
• Age • Gender
• CAD • Prior cholesterol value
Male, age ≤ 73, CAD present, cholesterol < 250 or unknown
Visit 1
• Brief questionnaire
• Fasting lipid profile 1
1-2 weeks
Lipid profile: meets criteria *
Visit 2
• Fasting lipid profile 2
• Routine lab screen
1-2 weeks
Lipid profile : meets criteria *
No abnormalities on lab screen
Visit 3
• Informed consent
• History/PE
• Radionuclide ventriculogram **
• Fasting lipid profile 3
1-2 weeks
All entrance criteria met
Baseline Visit
• Randomization
• History/PE
• ECG
• Fasting lipid profile 4
• Special and safety lab tests
• Medication dispensed

FIGURE 1. Screening protocol. CAD = coronary artery disease; ECG = electrocardiogram; PE = physical examination; *see Table I; **see Figure 2.

Consenting, eligible patients return 1 to 2 weeks after this final screening visit for the baseline visit. After a patient's eligibility is verified by the coordinating center, the subject is randomized according to a permuted block design. Randomization is stratified by center to achieve balance between treatment groups within each center. Baseline data (history, physical examination, electrocardiogram, blood for lipids, special studies and safety tests, quality of life and dietary questionnaires) are obtained and the patient receives his study medication. The average of the lipid values from this and from the final screening visit are used to define the patient's baseline lipid status.

During the screening process patients are asked to keep their weight stable, continue their usual medications, and maintain their smoking and exercise habits. Patients who make significant alterations in any of these are not eligible; they may, however, be rescreened once a minimum of 6 weeks later.

Lipid analysis: To minimize the effects of biologic variation on lipid results, blood samples are obtained according to a standard protocol described in the operations manual. Patients must be fasting for 12 to 14 hours before venipuncture and must refrain from alcohol for

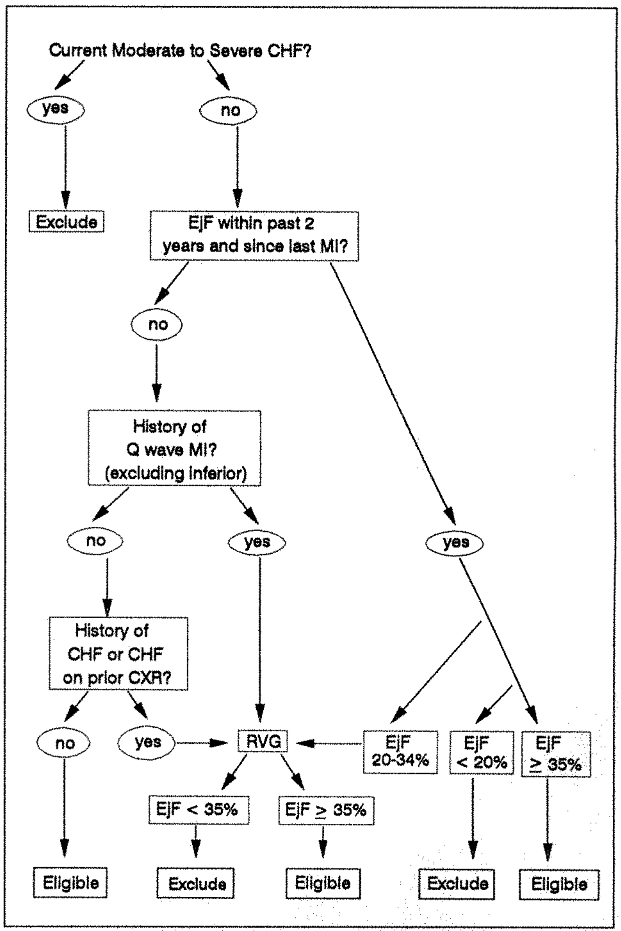
Current Moderate to Severe CHF?
yes
no
Exclude
EjF within past 2 years and since last MI?
no
History of Q wave MI? (excluding inferior)
no
yes
yes
History of CHF or CHF on prior CXR?
no
yes
RVG
EjF 20-34%
EjF < 20%
EjF ≥ 35%
EjF < 35%
EjF ≥ 35%
Eligible
Exclude
Eligible
Exclude
Eligible

FIGURE 2. Algorithm for assessing left ventricular function. CHF = congestive heart failure; CXR = chest radiograph; EjF = left ventricular ejection fraction; MI = myocardial infarction; RVG = radionuclide ventriculogram.

≥24 hours. Phlebotomy is deferred if the patient has been ill or hospitalized within the previous 2 weeks. Blood is obtained after the patient has been seated for ≥5 minutes. Tourniquet time is minimized. Screening samples are analyzed in the local clinical laboratories; the 2 baseline (from the final screening visit and the baseline visit) and all subsequent samples are analyzed by a central lipid laboratory.

Blood destined for the central lipid laboratory is drawn into tubes containing ethylenediaminetetraacetic acid. The plasma is separated by centrifugation and frozen at –20°C. Samples are packed with dry ice in insulated containers and sent by overnight mail to the central lipid laboratory. Plasma cholesterol and triglyceride concentrations are measured by enzymatic assays using a biochromatic analyzer (Abbott Spectrum CCX, Abbott Diagnostics, Irving, Texas). HDL cholesterol is isolated from the supernatant, after apolipoprotein B-containing particles are precipitated from the plasma with dextran sulfate magnesium.[44] LDL cholesterol is calculated by the method of Friedewald et al.[45] The HIT central lipid laboratory participates in the Centers for Disease Control–National Heart, Lung, and Blood Institute Lipid Standardization Program and serves as a regional network reference laboratory for that program.

After randomization, lipid results are not disclosed to patients or to study personnel. To maintain this blind, only the coordinating center is able to link central laboratory measurements to an individual patient.

In addition to the standard lipid profile, the following analyses will be performed at baseline and periodically during follow-up: HDL_2 and HDL_3, by differential dextran sulfate magnesium precipitation[46]; lipoprotein (a) by an enzyme-linked immunoabsorbent assay (Terumo Medical Corporation, Elkton, Maryland); plasma insulin, by a double antibody radioimmunoassay[47]; and apolipoproteins A_1 and B, by immunoturbidometric procedures (INCSTAR Corporation, Stillwater, Minnesota). Extra plasma samples will be maintained frozen at -70°C in the central laboratory for additional analyses.

Follow-up: Subjects are seen in the clinic every 3 months for the duration of the trial (maximum 7 years, minimum 5 years). At the first follow-up visit (1 month after randomization) patients receive their first formal education in the American Heart Association step I diet with a particular emphasis on achieving ideal body weight. They are also counseled to stop smoking and to participate in a regular exercise program. At each subsequent visit this advice is reinforced. Written and videotaped materials are provided to aid in lifestyle education. Dietary habits are monitored annually by a validated questionnaire (adapted from the Northwest Lipid Research Clinic's Fat Intake Scale).

Blood for lipids and safety monitoring is obtained every 6 months. Once a year a history and physical examination are performed and an electrocardiogram obtained. At every visit inquiry is made about possible adverse effects, occurrence of end points or other relevant clinical occurrences, changes in lifestyle and medications, and compliance with study medication. Compliance is assessed by tablet count performed without the subject's knowledge.

During follow-up, we will monitor subjects' affective states with a standardized questionnaire (the Health Insurance Study-General Well-Being Schedule[48]) in order to assess possible changes in mood or behavior that may underlie the association between cholesterol reduction and increased incidence of violent and accidental deaths noted in previous studies.[49]

Patients are followed until death, refusal of further visits, or the scheduled conclusion of the study. Those not taking drugs and those who have sustained a nonfatal myocardial infarction continue to be followed with periodic clinic visits. Patients are asked to continue their study medication after a nonfatal myocardial infarction.

To ensure that patients in this study receive appropriate care should they become significantly hypercholesterolemic or hypertriglyceridemic during follow-up, threshold values for total cholesterol (260 mg/dl) and fasting triglycerides (500 mg/dl) have been established. Any value above these levels (as measured at the central laboratory) will prompt the coordinating center to notify the local principal investigator and request that the patient be referred for intensive dietary counseling. Further action is discretionary but discontinuation of study medication and/or initiation of other lipid medication is discouraged (to minimize "crossovers" between the 2 treatment groups). With an anticipated mean baseline total cholesterol of 180 mg/dl and triglycerides of 175 mg/dl (based on pilot data), we expect that these threshold values will rarely be exceeded.

End points: The primary end point is defined as the time to occurrence of a nonfatal myocardial infarction or CAD death. Thus, if a patient experiences a myocardial infarction followed later by CAD death, the end point is the time to myocardial infarction; the death will be included in the secondary analysis of overall mortality. This study was not designed to have sufficient power to detect a difference between the treatment groups in either all-cause mortality or CAD mortality alone. With a sample size of 2,500 (see later), this trial will have only a 50% power to detect a 15% reduction in all-cause mortality.

Explicit criteria for the diagnoses of nonfatal myocardial infarction and CAD death were developed. Myocardial infarctions are diagnosed by a combination of standard electrocardiographic, cardiac enzyme and symptom criteria. Silent myocardial infarctions are included and are diagnosed by either the appearance of a diagnostic Q wave (Minnesota code patterns ED1 to 4[50]) or by the combined presence of an equivocal Q wave (Minnesota code patterns ED5 to 7[50]) plus a documented regional wall motion abnormality in the corresponding anatomic location. CAD death includes fatal myocardial infarction, fatal invasive cardiac procedure or surgery, and fatal congestive heart failure. Resuscitated cardiac arrests are also included provided no nonatherosclerotic cause is identified.

All primary end points are adjudicated (with use of a standard algorithm based on the diagnostic criteria) by the end points committee after reviewing relevant clinical information including electrocardiograms, discharge summaries, laboratory reports, and so forth. The committee is unaware of treatment assignment and lipid results. All electrocardiograms are read at a central electrocardiographic coding center using the Minnesota code.[51] Follow-up electrocardiograms are read for serial changes using the baseline electrocardiogram for comparison.[52]

In addition to CAD death and myocardial infarction, other relevant clinical occurrences that will be evaluated include noncardiac death (in particular death due to cancer and violent or accidental causes), unstable angina, congestive heart failure, coronary artery revascularization procedures, cerebrovascular and peripheral vascular disease.

Detection of end points occurs through regular follow-up visits, electrocardiograms obtained annually and on report of suspicious symptoms, and routine examination of hospital census reports. For patients no longer participating in regular follow-up, hospitalizations for myocardial infarction at the local site can be detected through a computerized database (Patient Treatment File). In addition, survival status can be ascertained through the Department of Veterans Affairs' Beneficiary Identification and Records Locator Subsystem.

Sample size and trial duration: Sample size for comparing the difference between 2 event curves by the log- rank statistic was calculated using the method of Lakatos[53] after accounting for complex trial conditions such as time-varying hazard rates, staggered entry, losses to follow-up and noncompliance. A sample size of 2,500 and a 7-year trial duration (with a 2-year intake period) is estimated to provide 90% power to detect a 20% reduction in the primary end point rate at the 2-sided 0.05 significance level. The following assumptions were made: (1) cumulative end point rate in the control group of 30% over 7 years (based on a literature review suggesting an event rate of between 5 and 6%/year[54]); (2) cumulative noncompliance rate (i.e., patient stops taking gemfibrozil and does not start a comparable therapy) of 30% over 7 years (estimate based on the experience in the Helsinki Heart Study[24]); (3) cumulative drop-in rate (i.e., control patient starts taking gemfibrozil or comparable therapy) of 12% over 7 years; (4) 2-year lag before full treatment benefit is observed (as seen in comparable trials[24,55]); (5) intention-to-treat analysis (i.e., a patient is counted in the group to which he was randomized regardless of adherence to therapy).

Sensitivity studies were conducted to evaluate the impact of misspecification of design assumptions on sample size and power. Even if noncompliance and loss to follow-up are substantially higher than predicted, there is only a small decrease in power. If the observed cumulative end point rate in the control group is 25% instead of 30%, the study will still have 85% power. If the observed percent reduction in end points is 16% instead of 20%, the study's power will decline to 75%. If the cumulative end point rate in the control group is substantially lower than expected, the sample size may have to be increased or follow-up extended, or both, to observe a sufficient number of end points.

Data analysis: PRIMARY END POINT: The primary end point is defined as the time to occurrence of a nonfatal myocardial infarction or CAD death. Two-tailed treatment comparisons for the primary end point will be made by the log-rank statistic. Primary treatment comparisons will be made with an intention-to-treat analysis. Cumulative event rates will be calculated by the product-limit life-table method. The Cox life-table regression method will be used to calculate estimates of relative risk, provided the model fits the data. Significance levels will be set in accordance with the plan for monitoring the study (see later). The overall significance level will be 5%.

SECONDARY OBJECTIVES: Cox proportional-hazard models will be used to evaluate the relation between HDL cholesterol level and risk of CAD end points while adjusting for the effects of other lipids and baseline parameters. The effect of gemfibrozil versus placebo on lipid levels, both before and after adjustment for baseline characteristics, will be evaluated using appropriate statistical methods for repeated measures. Effects will be examined descriptively for subsets of patients (e.g., age, smoking status, ß-blocker use, and so forth). Other relevant clinical occurrences (see before) will be descriptively evaluated; this study is not expected to be large enough to detect differences between treatment groups for these events. Statistical analyses of secondary hypotheses will be performed at the 1% level of significance to control for multiplicity of comparisons.

Trial structure and organization:* The HIT was planned and is being conducted under the auspices of the Cooperative Studies Program of the Department of Veterans Affairs Medical Research Service. Twenty Department of Veterans Affairs medical centers throughout the United States are participating in the trial. The Cooperative Studies Program Coordinating Center in West Haven, Connecticut coordinates the operation of the trial.

The study group, consisting of the co-chairs, biostatistician, research pharmacist, investigators and consultants, meets annually to review the trial's progress; its Executive Committee makes all decisions regarding operational aspects of the trial. The Human Rights Committee of the Cooperative Studies Program Coordinating Center approved the protocol and monitors the trial regularly to assure protection of the rights and safety of participants. In addition, the Institutional Review Board at each participating center approved the protocol and monitors the study.

The Data Monitoring Board, consisting of 7 experts in the fields of cardiology, lipid metabolism, cardiovascular epidemiology and/or biostatistics, has overall responsibility for approving the protocol, monitoring the progress of the trial, and analyzing interim data for efficacy and safety. This group has the authority to recommend to the Chief of the Cooperative Studies Program that the trial be stopped (e.g., for inability to recruit sufficient patients or for compelling internal or external evidence of either efficacy or toxicity). The board has elected to monitor the primary end point of the study using the method of stochastic curtailment.[56] The study may terminate early if the conditional probability of rejecting the null hypothesis at the scheduled end of the study, given the current data, is above or below prespecified values determined by the board. The monitoring procedure is a guide for the complex decisions the board must make when considering early termination of the study.

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*See Appendix.

Corporate support: At its first meeting the planning committee decided, for the reasons detailed previously, to use gemfibrozil for the trial. Parke-Davis (division of Warner Lambert Co.) subsequently offered to provide the drug, matching placebo, and partial funding for the trial. In accordance with requirements of the Food and Drug Administration, the company reviews adverse events possibly related to the drug and provides clinical monitors who audit data collection at each center. The company has no knowledge of treatment assignments and no access to lipid results or end points data. The co-chairs, participating investigators, and members of the Data Monitoring Board all indicated in writing that they have no involvement with the corporate sponsor that constitutes a conflict of interest with regard to their participation in this trial.

APPENDIX

Participating Department of Veterans Affairs Medical Centers: *Ann Arbor, Michigan:* William Kou,* G. B. John Mancini,* Scott Sample, Nicole Champagne; *Boston, Massachusetts:* William E. Boden,* Carol Chapin, Dorothy Gilroy, Nancy Aicardi; *Chicago, Illinois:* Mary Ann Papp,* Sue Stanford, Sandy Monreal; *Cincinnati, Ohio:* Laura F. Wexler,* Judy Shaffer,* Elizabeth Snow, Karen Johnson; *Fresno, California:* Prakash C. Deedwania,* Eva Murphy, Joyce King; *Houston, Texas:* Douglas L. Mann,* Peter Kuo, Carl Tyler, Donna Espadas; *Huntington, West Virginia:* Robert C. Touchon,* Ken Peart, Mark Babb; *Lexington, Kentucky:* James W. Anderson,* Belinda Smith, Lorraine Buchanan, Jo Ellen Logan; *Little Rock, Arkansas:* Fred H. Faas,* Sharon Thomas, Keena Ridings; *Long Beach, California:* Moti L. Kashyap,* Nancy Downey, Rebecca Knight, Jahandar R. Saleh; *Louisville, Kentucky:* S. Abraham Joseph,* Ellis Samols,* Diane Kinny, Loretta Pignatora; *Manchester, New Hampshire/White River Junction, Vermont:* Michael Mayo-Smith,* Christopher Nice,* Margaret Carson, Linda Lavoie; *Memphis, Tennessee:* Marshall B. Elam,* Gale Rutan,* Linda Harris, Judy Pinson, Rhonda Childress; *Milwaukee, Wisconsin:* Gordon Schectman,* Sue Ristow, Carol Parker; *Minneapolis, Minnesota:* Timothy J. Wilt,* Linda Schlasner, Debbie Rootes; *Portland, Oregon:* Henry DeMots,* Lori Gray, Susan Bagnoli; *Salem, Virginia:* Ali Iranmanesh,* Douglas C. Russell,* Sara Clary, Liza Wertz; *San Juan, Puerto Rico:* Esteban Linares,* Maria S. Velazquez, Maria De Lourdes Cruz; *Washington, D.C.:* Vasilios Papademetriou,* Madeline Metcalfe, Patty Dandenau; *West Los Angeles, California:* Jerome M. Hershman,* Bramah N. Singh,* Patricia McCloy, Katherine Goddart.

Co-Chairs: Department of Veterans Affairs Medical Center, Minneapolis, Minnesota: Hanna Bloomfield Rubins (co-chair), Joanne Karvonen; Department of Veterans Affairs Medical Center, Boston, Massachusetts: Sander J. Robins (co-chair).

Department of Veterans Affairs Cooperative Studies Program Coordinating Center: West Haven, Connecticut: Dorothea Collins (Chief), Marika K. Iwane (study biostatistician), Rae Bartozzi, Cindy Cushing, Joan Derrico, Kathy Newvine.

Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center: Albuquerque, New Mexico: Mike R. Sather (Chief), Carol L. Fye (clinical research pharmacist), Mariann Drago, Roy Fetter, William Gagne.

Central Lipid Laboratory: Lipid Research Laboratory, Endocrinology Division, Department of Medicine, New England Medical Center Hospitals, Boston, Massachusetts: Ernst J. Schaefer (Director), Judith R. McNamara.

Electrocardiographic Coding Center: University of Minnesota, School of Public Health, Division of Epidemiology, Minneapolis, Minnesota: Richard S. Crow (Director), Cheryl Swanson.

Nutrition Consultant: Department of Veterans Affairs Medical Center, Richmond, Virginia: Kathleen Smith.

Committees: *Data Monitoring Board:* Thomas A. Pearson (Chair), Antonio M. Gotto (Vice Chair), Kent R. Bailey, Barry R. Davis, Alfred F. Parisi, Basil M. Rifkind, Robert Zelis. *Executive Committee:* Hanna B. Rubins and Sander J. Robins (Co-Chairs), William E. Boden, Marshall B. Elam, Carol L. Fye, David J. Gordon, Marika K. Iwane, Ernst J. Schaefer, Gordon Schectman, Timothy J. Wilt, Janet T. Wittes. *Endpoints Committee:* Marshall B. Elam (Chair), Richard Crow, Henry DeMots, Esteban Linares, Gale Rutan. *Planning Committee:* Hanna B. Rubins and Sander J. Robins (Co-Chairs), William E. Boden, Marshall B. Elam, Carol L. Fye, David J. Gordon, Marika K. Iwane, Raj Lakshman, Ernst J. Schaefer, Gordon Schectman, Janet T. Wittes.

Acknowledgment: We thank Frank Lederle, MD, Kristin Nichol, MD, and Jeffrey Rubins, MD, for their review of a previous draft of the manuscript, and Joanne Karvonen for manuscript preparation.

REFERENCES

1. Grundy SM, Goodman DS, Rifkind BM, Cleeman JI. The place of HDL in cholesterol management: A perspective from the National Cholesterol Education Program. *Arch Intern Med* 1989;149:505–510.
2. Rutherford JD, Braunwald E. Chronic ischemic heart disease. In: Braunwald E, ed. Heart Disease. 4th ed. Philadelphia: WB Saunders, 1992:1292–1364.
3. Criqui MH. Cholesterol, primary and secondary prevention, and all-cause mortality. *Ann Intern Med* 1991;115:973–976.
4. Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 1990;322:1700–1707.
5. Franzen J, Johansson BW, Gustafson A. Reduced high density lipoproteins as a risk factor after acute myocardial infarction. *Acta Med Scand* 1987;221:357–362.
6. Miller M, Mead LA, Kwiterovich PO, Pearson TA. Dyslipidemias with desirable plasma total cholesterol levels and angiographically demonstrated coronary artery disease. *Am J Cardiol* 1990;65:1–5.
7. Ginsburg GS, Safran C, Pasternak RC. Frequency of low serum high-density lipoprotein cholesterol levels in hospitalized patients with ''desirable'' total cholesterol levels. *Am J Cardiol* 1991;68:187–192.

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*Principal Investigator.

8. Genest JJ, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. *Am J Cardiol* 1991;67:1185–1189.

9. Lavie CJ, Milani RV. National Cholesterol Education Program's recommendations, and implications of "missing" high-density lipoprotein cholesterol in cardiac rehabilitation programs. *Am J Cardiol* 1991;68:1087–1088.

10. Rubins HB, Schectman G, Wilt TJ, Iwane MK. High prevalence of isolated low HDL-cholesterol in community-living men with coronary heart disease. *Arch Intern Med;* in press.

11. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988;148:36–69.

12. Triglyceride, high density lipoprotein, and coronary heart disease. Reprinted from *NIH Consens Dev Conf Consens Statement* 1992;February 26–28;10(2).

13. Barr DP, Russ EM, Eder HA. Protein-lipids relationships in human plasma. II. In atherosclerosis and related conditions. *Am J Med* 1951;11:480–493.

14. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. *Am J Med* 1977;62:707–714.

15. Miller NE, Thelle DS, Forde OH, Mjos OD. The Trømso Heart Study: high density lipoprotein and coronary heart-disease: a prospective case control study. *Lancet* 1977;1:965–968.

16. Gordon DJ, Rifkind BM. High-density lipoprotein — the clinical implications of recent studies. *N Engl J Med* 1989;321:1311–1316.

17. Assman G, Schulte H. Prospective Cardiovascular Meunster Trial. Heidelberg: Pascienta Verlag, 1986.

18. Kannel WB, Castelli WP. Cholesterol in the prediction of atherosclerotic disease: new perspectives based on the Framingham Study. *Ann Intern Med* 1979;90:85–91.

19. Stampfer MJ, Sacks MD, Slvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991;325:373–381.

20. Manninen V, Elo O, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternak A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988;260:641–651.

21. Gordon DJ, Knoke J, Probstfield JL, Superko R, Tyroler HA. High-density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men: The Lipid Research Clinics Coronary Primary Prevention Trial. *Circulation* 1986;74:1217–1225.

22. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233–3240.

23. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao X, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289–1298.

24. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237–1245.

25. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation* 1989;79:8–15.

26. Glomset JA. The plasma lecithin:cholesterol acyltransferase reaction. *J Lipid Res* 1968;9:155–167.

27. Gwynne JT. HDL and atherosclerosis: an update. *Clin Cardiol* 1991;14(suppl I):I-17–I-24.

28. Tall AR. Plasma high density lipoproteins: metabolism and relationship to atherogenesis. *J Clin Invest* 1990;86:379–384.

29. Slotte JP. HDL receptors and cholesterol efflux from parenchymal cells. *Eur Heart J* 1990;11(suppl E):212–217.

30. Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. *J Clin Invest* 1990;85:1234–1241.

31. Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. *Nature* 1991;353:265–267.

32. Gianturco SH, Bradley WA. A cellular basis for the atherogenicity of triglyceride-rich lipoproteins. *Atherosclerosis* 1991;22:9–14.

33. Austin MA, King M, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. *Circulation* 1990;82:495–506.

34. Mitropoulos KA. Hypercoagulability and factor VII in hypertriglyceridemia. *Stat Med* 1988;14:246–252.

35. Simpson HCR, Meade TW, Stirling Y, Mann JI, Chakrabarti R, Woolf L. Hypertriglyceridaemia and hypercoagulability. *Lancet* 1983;1:786–789.

36. Wenger NK, Roberts R. Clinical aspects of coronary heart disease. In: Eaker ED, Packard B, Wenger NK, Clarkson TB, Tyroler HA, eds. Coronary Heart Disease in Women. New York: Haymarket Doyma, 1987:22–28.

37. American Heart Association. Fact Sheet on Heart Attack, Stroke, and Risk Factors. Dallas, TX: American Heart Association, 1991.

38. Abbott RD, Wilson PWF, Kannel WB, Castelli WP. High density lipoprotein cholesterol, total cholesterol screening, and myocardial infarction. *Arteriosclerosis* 1988;8:207–211.

39. Jacobs DR, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence study. *Am J Epidemiol* 1990;131:32–47.

40. Pasco EA. Data on Female Veterans, Fiscal Year 1986. Office of Information Management and Statistics, Statistical Policy and Research Service, 1987.

41. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, Ellsworth NM, Terry RB, Haskell WL. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 1988;319:1173–1179.

42. Hunninghake DB. Drug treatment of dyslipoproteinemia. *Endocrinol Metab Clin North Am* 1990;19:345–360.

43. Vega GL, Grundy SM. Comparison of lovastatin and gemfibrozil in normolipidemic patients with hypoalphalipoproteinemia. *JAMA* 1989;262:3148–3153.

44. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg^{2+} precipitation procedure for quantification of high density lipoprotein cholesterol. *Clin Chem* 1982;28:1379–1388.

45. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–508.

46. Bachorick PS, Albers JJ. Precipitation methods for quantification of lipoproteins. *Methods Enzymol* 1986;129:78–100.

47. Boyd NE, Bolton WE, Brinkley BR. Microtubules and beta cell function: Effect of colchicine on microtubules and insulin secretion in vitro by mouse beta cells. *J Cell Biol* 1982;92:425–434.

48. Ware JE, Johnston SA, Davies-Avery A, Brook RH. Conceptualization and measurement of health for adults in the Health Insurance Study. vol III. Mental Health. R-1987/3-HEW, Rand Corporation, 1979.

49. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990;301:309–314.

50. ARIC Protocol, manual 5. Electrocardiography. Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina, Chapel Hill, NC.

51. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. Boston: John Wright/PSG Inc., 1982.

52. Crow RS, Prineas RJ, Jacobs DR, Blackburn H. A new epidemiologic classification system for interim myocardial infarction from serial electrocardiographic changes. *Am J Cardiol* 1989;69:454–461.

53. Lakatos E. Sample size determination in clinical trials with time-dependent rates of losses and noncompliance. *Controlled Clin Trials* 1986;7:189–199.

54. Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med* 1990;323:1112–1119.

55. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351–364.

56. Lan KKG, Simon R, Halperin M. Stochastically curtailed tests in long-term clinical trials. *Communications in Statistics C (Sequential Analysis)* 1982;1:207–219.

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Now you can help increase survival and prevent hospitalizations in many early symptomatic heart failure patients with Left Ventricular Dysfunction

SOLVD

Results from the largest and longest heart failure trial to date are in. And they demonstrate that enalapril — usually in combination with conventional therapy* — is superior to conventional therapy alone in increasing survival and preventing hospitalizations in symptomatic mild-to-moderate heart failure with left ventricular dysfunction (LVD).[1]

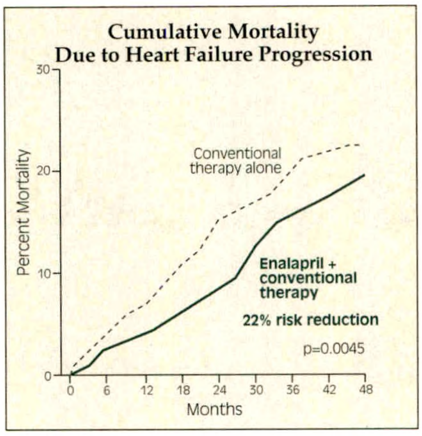
SOLVD — a 4-year survival study of enalapril in mild-to-moderate heart failure (n=2569)

The Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial, conducted by the NIH, evaluated 2569 heart failure patients (98% NYHA Classes I through III) with ejection fractions ≤0.35. These patients were selected from over 39,000 screened patients. (Another 4228 patients who were asymptomatic were selected for a second SOLVD trial and 6336 patients with ejection fractions <0.45 were included in a registry.) Diseases that excluded patients from enrollment in the Treatment Trial included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2.5 mg/dL), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis, and constrictive pericarditis.

This double-blind, placebo-controlled, multicenter trial lasted 4 years (average follow-up was 41.4 months). All patients received conventional therapy and were randomized to add either enalapril or placebo.

Patients live longer

SOLVD demonstrated a clear survival benefit for many of these symptomatic patients receiving enalapril compared with conventional therapy alone. All-cause mortality was reduced 11%. The largest mortality reduction occurred in deaths due to heart failure progression...a risk reduction of 22%.


Cumulative Mortality Due to Heart Failure Progression

Difference in mortality as early as 3 months

Mortality reductions with enalapril were observed as early as 3 months and throughout the entire study. The greatest benefit occurred during the first 24 months (19% reduction at the end of 24 months).

Patients hospitalized less

SOLVD demonstrated that enalapril reduced the number of hospitalizations for heart failure by 30% (p<0.001) — and that it reduced the number of readmissions by 33% (p<0.001).

The authors noted: for every 1000 heart failure patients similar to those in the study, 350 hospitalizations could be prevented over 3 years by adding enalapril.

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By adding VASOTEC early to conventional therapy, you can help to significantly improve symptoms, increase survival, and prevent hospitalizations in many of your patients with symptomatic mild-to-moderate heart failure with LVD. The earlier you prescribe VASOTEC in appropriate patients, the sooner they may realize the benefits demonstrated in the SOLVD study.

VASOTEC®
(ENALAPRIL MALEATE)

In Symptomatic
Heart Failure,
Usually with
Diuretics
and Digitalis

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*Diuretics (86% of patients in the enalapril group; 85% in the placebo group) and digitalis (66% of patients in the enalapril group; 68% in the placebo group), as well as drugs other than ACE inhibitors.

[1] The SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure, N. Engl. J. Med. *325(5)*:293-302, August 1, 1991.

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USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASOTEC should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

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USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASOTEC should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Contraindications: VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASOTEC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASOTEC should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats) and 50 times (in rabbits) the maximum recommended human dose.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients: Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Pregnancy: Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Body As A Whole: Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*).

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia, impotence.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings: Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or congestive heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

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Comparison of Effects of Propranolol Versus Pindolol on Sinus Rate and Pacing Frequency in Sick Sinus Syndrome

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Beta blockers in patients with sick sinus syndrome (SSS) may prevent supraventricular arrhythmias, systemic hypertension and myocardial ischemia, but may cause excessive depression of sinus node function. In 8 patients with SSS and a permanent pacemaker, the effect of chronic oral pindolol on sinus rate and pacing frequency was compared with that of propranolol in a double-blind crossover trial. In all patients the pacemaker was programmed to a rate of ≤50 beats/min. Holter monitors, obtained at baseline and on each drug, were used to calculate peak ambulatory sinus rate, number of paced beats per day, maximal number of paced beats per hour, and percentage of hours with paced beats. The peak sinus rate with pindolol therapy was 24% higher than with propranolol ($p = 0.001$). During pindolol therapy, the number of paced beats per day and maximal paced beats per hour were reduced 54% ($p = 0.04$) and 61% ($p = 0.02$), respectively, compared with propranolol. Patients with SSS who require β-blocker therapy for tachycardia, systemic hypertension or angina pectoris may have less bradycardia when treated with pindolol rather than propranolol. Beta blockers like pindolol, which cause less sinus node depression, may obviate the need for prophylactic permanent pacemakers in patients with SSS, and may help to prevent chronotropic incompetence and pacemaker syndrome in patients already treated with a VVI device.

(Am J Cardiol 1993;71:53–56)

Patients with sick sinus syndrome (SSS) sometimes require therapy for atrial arrhythmias, systemic hypertension or myocardial ischemia. Whereas β-adrenergic blocking drugs have proven value in treating these problems, β blockers may also prolong sinus cycle length and sinus node recovery times, exacerbate bradycardia, and cause chronotropic incompetence in patients with SSS.[1–5] A β blocker without these adverse effects would be a desirable therapeutic agent. Theoretically, β blockers like pindolol with intrinsic sympathomimetic activity should cause less depression of sinus node function than β blockers like propranolol without intrinsic sympathomimetic activity. The effects of these agents on bradycardia in patients with SSS have never been compared. Therefore, to test this hypothesis we studied the effects of pindolol and propranolol in patients with SSS using a prospective, randomized, double-blind, crossover study design.

METHODS

Eight patients with SSS and permanent programmable pacemakers followed by the Arrhythmia Service at the Brigham and Women's Hospital were enrolled in a research protocol approved by the Committee for the Protection of Human Subjects from Research Risks. Each patient gave informed consent at the time of enrollment.

Patient selection: Patients aged ≥21 years who were previously treated with a permanently implanted rate programmable pacemaker for SSS and who could tolerate a programmed rate of ≤50 beats/min were eligible for the protocol. Patients enrolled in the study had undergone implantation of a permanent pacemaker ≥3 weeks and as long as 4 years before entry in the study. Patients were excluded if there was a history of acute myocardial infarction within 6 months, congestive heart failure, unstable angina, insulin-dependent diabetes mellitus, aortic stenosis, alcohol or drug abuse, asthma or chronic obstructive pulmonary disease, or uncontrolled hypertension. Patients treated concomitantly with β- and α-blocking agents antiarrhythmic agents, verapamil, monoamine oxidase inhibitors, adrenolytic drugs, or psychotropic agents also were excluded from the study.

Study design: The study consisted of a 7-week trial plus an initial 1 week washout period (Table I). At the beginning of the 1-week washout phase, each patient's pacemaker was programmed to 50 pulses/min, or more

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From the Cardiac Arrhythmia Service and Clinical Electrophysiology Laboratory, Brigham and Women's Hospital, Boston, Massachusetts. This study was supported in part by a grant from Sandoz Research, Inc., East Hanover, New Jersey; and Training Grant HL-07604 from the National Institutes of Health, Bethesda, Maryland. Manuscript received May 26, 1992; revised manuscript received and accepted August 3, 1992.

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TABLE I Study Design

			Period I				Period II		
	Initial Washout Period	Randomization*	Active Treatment		Drug Taper	Placebo Washout	Active Treatment		Drug Taper
Week	−1†	0	1	2†	3	4	5	6†	7
		Sequence 1	Pindolol, 5 mg capsule TID			Placebo, 1 capsule TID	Propranolol, 40 mg capsule TID		
		Sequence 2	Propranolol 40 mg capsule TID			Placebo, 1 capsule TID	Pindolol, 5 mg capsule TID		
			← Double-blind →			← Single-blind →	← Double-blind →		

*Pacemaker programmed to race ≤ 50 pulses/min.
†Continuous Holter monitoring (48 hours) at the conclusion of this week.
TID = Three times daily.

TABLE II Patient Profiles

Pt.	Age (yr) & Sex	DM	SH	CAD	Angina	CABG
1	69 F	0	0	+	0	+
2	66 F	+	+	0	0	0
3	85 F	+	0	+	0	+
4	79 M	0	0	+	+	0
5	84 F	0	+	0	0	0
6	79 F	0	0	0	0	0
7	76 F	0	0	0	0	0
8	71 M	0	0	0	0	0

CABG = status after coronary artery bypass grafting surgery; CAD = coronary artery disease documented by coronary angiography; DM = diabetes mellitus; SH = systemic hypertension; + = present; 0 = absent.

slowly for patients with intrinsic heart rates less than this rate. At the end of the washout period and upon satisfying the entry criteria qualified patients were entered into the protocol and then were randomly assigned to sequence 1 or 2. Patients assigned to sequence 1 received pindolol (5 mg capsule orally, 3 times daily) during period I active treatment (weeks 1 to 2) and then propranolol (40 mg capsule orally, 3 times daily) during period II active treatment (weeks 5 to 6). Patients assigned to sequence 2 received pindolol and propranolol in the reverse order. After each active treatment period the drugs were tapered over several days. After period I drug taper, patients were treated for 1 week with placebo (1 capsule orally, 3 time daily). The study medications were administered in a double-blind manner, and placebo was administered in single-blind fashion. The study was concluded with period II active treatment (weeks 5 to 6), and then with the period II drug taper (week 7). Patients underwent 2 sequential 24-hour Holter monitor recordings (Picker International, model 7300, Bedford, Massachusetts) on the last 2 days of the initial washout period and the last 2 days of each active treatment period. A Del Mar Avionics (model 9401, Irvine, California) Holter monitor analysis and printing system was used. The entire printout of all Holter monitor recordings were manually evaluated for paced beats by experienced Holter technicians. The minimal and maximal ambulatory sinus heart rate, total number of paced beats per day, average paced beats per hour, minimal and maximal paced beats per hour, and percentage of hours with paced beats were then calculated. Baseline physical examination, electrocardiogram, chest x-ray and standard laboratory examinations were obtained at week 1 (Table I). Cardiovascular evaluations, electrocardiograms, concomitant medical therapy, patient's symptom report and adverse reactions were obtained at the conclusion of each treatment phase.

Data analysis: Holter monitoring data under different treatment conditions were examined by an analysis of variance with repeated measures. Statistical significance of differences in heart rate and pacing parameters were then determined by paired *t* test. A p value ≤ 0.05 was considered significant (≤ 0.0167 after Bonferroni correction for multiple comparisons).

RESULTS

Clinical characteristics: Clinical profiles of the 8 study subjects are summarized in Table II. Of the 3 patients with coronary artery disease, 2 had remote coronary artery bypass grafting surgery and 1 had stable angina. Two patients had non–insulin-dependent diabetes.

Serial Holter examinations: Mean heart rate and mean pacing data are summarized in Table III. Mean peak ambulatory heart rate (± standard deviation) during usual daily activities was 82 ± 19 in the baseline state, 62 ± 9 during propranolol therapy, and 77 ± 14 during pindolol treatment. The heart rate reduction during propranolol therapy compared with baseline was statistically significant ($p < 0.01$), whereas the reduction with pindolol therapy was not ($p = 0.18$). The mean peak ambulatory heart rate was 24% greater with pindolol than with propranolol ($p = 0.001$). Compared with baseline, treatment with propranolol was not associated with a greater total number of paced beats per day. However, during pindolol therapy patients had 54% fewer paced beats per day than during propranolol therapy ($p = 0.04$). When patients were treated with pindolol the maximal number of paced ventricular beats per hour was 61% less during the baseline period or during propranolol treatment ($p = 0.04$ and 0.02, respectively). There was also a trend suggesting that patients were paced in 14% more of the hours during the baseline state and 34% more during propranolol therapy than during pindolol treatment ($p = 0.07$ and 0.09, respectively). There was no difference in the minimal ambulatory sinus rate or the minimal number of paced beats per hour among the 3 treatment conditions.

DISCUSSION

The theoretical benefit of therapy with β blockers with intrinsic sympathomimetic activity, like pindolol, relates to the positive chronotropic effects of these agents in vitro[6] and in various disease states.[7–11] Beta blockers with intrinsic sympathomimetic activity demonstrate positive chronotropic effects on isolated atrial tissue.[6] These agents tend to increase slightly low pretreatment heart rates and slightly lower rapid pretreatment heart rates in patients with coronary artery disease or hypertension.[7,8] Nocturnal bradycardia, which is aggravated by conventional β blockers, is improved by β blockers that have intrinsic sympathomimetic activity.[9–11] Bradycardia in patients with atrial fibrillation with rapid ventricular response rates is a common adverse effect of medical therapy. However, there is only limited published experience with β blockers with intrinsic sympathomimetic activity for prevention of excessive bradycardia in this patient population.[12–14] Additionally, some patients with sinus node dysfunction have demonstrated reduced pacemaker dependency when treated with pindolol rather than a placebo.[15] This study is the first to demonstrate that treatment of SSS patients with a β blocker that possesses intrinsic sympathomimetic activity may result in less bradycardia than treatment with a conventional β blocker.

The dose of propranolol (120 mg/day) and pindolol (15 mg/day) used in the present study were chosen to provide approximately equal degrees of β-adrenergic receptor blockade, based on published reports that pindolol is 5 to 10 times more potent a β blocker than propranolol.[16] The doses used in this study are also similar to the usual starting doses of these drugs as they are used clinically. Whether the diminution of bradycardia in elderly patients taking pindolol that was observed in the present study would also be observed in younger persons or with different doses of pindolol and propranolol cannot be inferred from our data. Our data are also limited by the small sample size and need to be confirmed by larger studies. The results suggest that patients with SSS who require β-blocker therapy to control tachycardia, systemic hypertension or angina may benefit from treatment with a β blocker like pindolol. It is possible that pacemaker syndrome and chronotropic incompetence in SSS patients with VVI pacemakers may be avoided with pindolol therapy. Additionally, some patients with SSS who require treatment with a β blocker may be able to avoid prophylactic permanent pacemaker implantation altogether if an agent with intrinsic sympathomimetic activity was used.

Acknowledgment: We gratefully acknowledge the excellent secretarial support of Mary Gillan, and the superb technical skills of Pamela Alvarez and Victoria Geschwind.

REFERENCES

1. Scheinman MM, Straus HC, Evans GT, Ryan C, Massie B, Wallace A. Adverse effects of sympatholytic agents in patients with hypertension and sinus node dys-

TABLE III Heart Rate and Pacing Data

Pt. No.	Peak Ambulatory Sinus Rate: Baseline	Peak Ambulatory Sinus Rate: Propranolol	Peak Ambulatory Sinus Rate: Pindolol	Paced Beats Per Day (× 1,000): Baseline	Paced Beats Per Day (× 1,000): Propranolol	Paced Beats Per Day (× 1,000): Pindolol	Average Paced Beats Per Hour: Baseline	Average Paced Beats Per Hour: Propranolol	Average Paced Beats Per Hour: Pindolol	Maximal Paced Beats Per Hour: Baseline	Maximal Paced Beats Per Hour: Propranolol	Maximal Paced Beats Per Hour: Pindolol	% of Hours with Paced Beats: Baseline	% of Hours with Paced Beats: Propranolol	% of Hours with Paced Beats: Pindolol
1	109	75	91	0	0.006	0	0	0.2	0	0	4	0	0	9	0
2	103	71	92	0.6	0.8	0.06	26	34	2	85	241	17	74	96	56
3	82	52	66	11.2	31.8	0.004	466	1,326	0.2	2,965	2,628	2	28	100	9
4	84	60	87	18.1	7.0	2.5	759	291	106	2,855	1,714	215	100	100	100
5	AF	AF	AF	13.6	46.7	20.2	569	1,945	840	2,005	2,979	1,992	100	100	100
6	62	58	65	17.0	14.5	0.9	707	604	39	2,785	2,981	510	79	85	50
7	62	52	58	41.2	53.9	49.6	1,717	2,246	2,066	2,981	2,941	2,971	100	100	100
8	73	64	78	3.9	6.0	0.7	163	248	28	1,492	1,480	178	100	100	96
Mean ± SD	82 ± 19	62 ± 9*	77 ± 14†	13.2 ± 13.3	20.1 ± 21.3	9.2 ± 17.7†	550 ± 556	837 ± 886	385 ± 737	1,196 ± 1,258‡	1,871 ± 1,225	736 ± 1,121†	73 ± 38	86 ± 32	64 ± 42

*Baseline versus propranolol, $p < 0.01$.
†Propranolol versus pindolol, $p \leq 0.04$.
‡Baseline versus pindolol, $p = 0.04$.
AF = atrial fibrillation (no sinus rhythm during Holter recording).

function. *Am J Med* 1978;64:1013–1020.

2. Strauss HC, Gilbert M, Svenson RH, Miller HC, Wallace AG. Electrophysiologic effects of propranolol on sinus node function in patients with sinus node dysfunction. *Circulation* 1976;54:452–459.

3. Narula OS, Vasquez M, Shantha N, Chuquimia R, Towne WD, Linhart JW. Effect of propranolol on normal and abnormal sinus node function. In: Bonke FI, ed. The Sinus Node. Structure, Function and Clinical Relevance. The Hauge: Martinus Nijhoff, 1978:112–128.

4. Hombach V, Braun V, Hopp HW, Gil-Sanchez D, Behrenbeck DW, Tauchert M, Hilger HH. Electrophysiological effects of cardioselective and non-cardioselective beta adrenoreceptor blockers with and without ISA at rest and during exercise. *Br J Clin Pharmac* 1982;13:285S–293S.

5. Frishman WH, Silverman R. Physiologic and metabolic effects. In: Frishman WH, ed. Clinical Pharmacology of Beta-Adrenoreceptor Blocking Drugs. New York: Appleton, 1980:15–34.

6. Kaumann AJ, Blinks JR. Beta-adrenoreceptor blocking agents as partial agonists in isolated heart muscle: dissociation of stimulation and blockade. *Naunyn Schmiedebergs Arch Pharmacol* 1980;311:237–248.

7. Rosenthal J, Kaiser H, Raschig A, Welzel D. Treatment of hypertension with a beta adrenoreceptor blocker. A multicenter trial with pindolol. *Br J Clin Pract* 1979;33:165–174.

8. Welzel D, Roskamm N, Samek L, Sturzenhofecker P. Pindolol postmyocardial infarction study: evaluation of the drug's antiarrhythmic and antianginal activity. *Am Heart J* 1982;104:512–515.

9. Leclercq JF, Rosengarten MD, Kural S, Attuel P, Coumel P. Effects of intrinsic sympathetic activity of beta blockers on SA and AV nodes in man. *Eur J Cardiol* 1981;12:367–375.

10. Floras JS, Jones JV, Hassan MO, Sleight P. Ambulatory blood pressure during once daily randomized double-blind administration of atenolol, metoprolol, pindolol and slow release propranolol. *Br Med J* 1982;285:1387–1392.

11. Fitscha P, Tiso B, Meisner W, Spitzer D. The effect of intrinsic sympathomimetic activity of beta adrenoreceptor blockers on circadian heart rate. *Br J Clin Pharmac* 1982;13:211S–215S.

12. Cristodorescu R, Rosu D, Deutsch G, Verdes A, Luca C. The heart rate slowing effect of pindolol in patients with digitalis resistant atrial fibrillation and heart failure. *Med Interne* 1986;24:207–15.

13. Reiffel JA. Improved rate control in atrial fibrillation. *Am Heart J* 1992;123:1094–1098.

14. James MA, Channer KS, Papouchado M, Rees JR. Improved control of atrial fibrillation with combined pindolol and digoxin therapy. *Eur Heart J* 1989;10:83–90.

15. Viersma JW, Vandenberg MP, VanGilst WH, Lie KI. Intrinsic sympathomimetic activity (ISA) of pindolol in patients with sinus node dysfunction. *Eur Heart J* 1986;7:42–46.

16. Hicks DC, Arbab AG, Turner P, Hills M. A comparison of intravenous pindolol and propranolol in normal man. *J Clin Pharmacol* 1972;12:212–216.

Morphologic Characteristics of Nonsustained Ventricular Tachycardia Detected During Holter Monitoring Associated with Atherosclerotic Coronary Artery Disease

Pablo Denes, MD

Nonsustained ventricular tachycardia (VT) is an important prognostic indicator of outcome in patients with organic heart disease. The morphologic features of nonsustained VT were examined by obtaining a derived 12-lead electrocardiogram (ECG_D) from a 24-hour Holter recording in 22 patients with nonsustained VT associated with coronary artery disease. A total of 60 nonsustained VT episodes were recorded. Of these, 20 were uniform and 40 were multiform. The mean rate of uniform episodes was faster (140 ± 32 vs 124 ± 16 beats/min; $p < 0.01$) and the duration longer (5.3 ± 2.0 vs 4.0 ± 1.0 beats; $p < 0.02$) than the multiform episodes. The majority (87%) of multiform episodes had only 2 different QRS configurations on the ECG_D. Four distinct patterns of QRS configurations were seen within individual multiform nonsustained VT runs: type I — the initial QRS complex has 1 morphology and all subsequent complexes have another configuration; type II — the initial and terminal QRS complex has similar configuration; type III — the first 2 QRS complexes have similar configuration and all subsequent complexes have another morphology; and type IV — the QRS complexes have alternating morphologic features. These 4 different patterns may be related to the mechanism of nonsustained VT (reentry versus automaticity). Patients with multiple episodes of nonsustained VT frequently had differing patterns and morphologic features between episodes. Further studies are needed to evaluate the clinical importance of these findings.

(Am J Cardiol 1993;71:57–62)

In a recent report, Drew et al[1] evaluated the accuracy of the derived 12-lead electrocardiogram (ECG_D) in the diagnosis of wide QRS complex tachycardia induced during cardiac electrophysiologic studies. In this study the derived 12-lead recording was helpful in establishing an accurate diagnosis of the mechanism of the tachycardia and also in demonstrating that the induced arrhythmia was similar to the spontaneously occurring tachycardia. The recently concluded Cardiac Arrhythmia Suppression Trial heightened the interest in the presence of nonsustained ventricular tachycardia (VT).[2] The role of electrophysiologic studies in the evaluation of patients with nonsustained VT is currently under study.[3] However, there is only limited information on the morphologic characteristics of nonsustained VT. The lack of information is due to the limited number of electrocardiographic leads that are available during monitoring.[4] In the present report we examined the morphologic features of nonsustained VT by reviewing the ECG_D findings in 22 patients who demonstrated 1 or more episodes of nonsustained VT on 24-hour Holter monitoring obtained with a 3-lead recording system.

METHODS

A total of 60 nonsustained VT episodes were analyzed in 22 patients (10 women and 12 men, mean age ± SD 72.5 ± 10 years [range 48 to 93 years]) undergoing 24-hour Holter monitoring at St. Paul-Ramsey Medical Center. All patients had coronary artery disease, and were in a clinically stable condition. Patients with acute myocardial infarction, significant electrolyte abnormalities or drug toxicity were not included. All but 2 patients, who had atrial fibrillation, were in sinus rhythm during the recording.

Holter recordings were obtained using the recording and analysis system developed by Zymed (model 1210, Zymed Medical Instrumentation, Camarillo, California). The recorder has 3 recording channels and the scanner can generate a derived 12-lead ECG on any section of the 3-channel recording. The ECG_D is a mathematic construct of a standard ECG, based on a 3 orthogonal lead system.[5–7] The lead system uses the E, A, I electrode positions of the Frank vectorcardiographic leads and an electrode S positioned over the upper end of the sternum.[5–7] The method has been published in detail by Dower et al.[5–7] The technician scanning the Holter tape obtains ECG_D on specific segments of the tape on request from the cardiologist reviewing the Holter find-

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ings. Arrhythmia detection is done by a computer-assisted system with operator interaction during processing.

Definitions: Nonsustained VT was defined as 3 consecutive ventricular premature complexes with an average rate of ≥100 beats/min.[2] Nonsustained VT episodes were defined as multiform when the QRS complexes during the episode of VT exhibited a different bundle branch block pattern or when they had a different (>30°) frontal plane axis. A nonsustained VT episode was defined as uniform if the QRS complexes during the VT exhibited similar bundle branch block pattern and frontal plane QRS axis. In patients with multiple (>1) episodes of nonsustained VT the morphology of the individual QRS complexes of each episode was evaluated and compared. Nonsustained VT with uniform morphology was defined as irregular if adjacent cycles varied >50%.

RESULTS

The length of nonsustained VT episode ranged from 3 to 10 beats and the average rate varied from 100 to 200 beats/min. Nine patients had single episodes and 13 had multiple episodes (2 to 8) recorded. There were 40 episodes of multiform and 20 episodes of uniform nonsustained VT.

Uniform nonsustained ventricular tachycardia: There were 20 episodes of uniform nonsustained VT, and 9 had left bundle branch block morphology. Six (75%) of these had a frontal plane QRS axis directed to the upper right quadrant (+180° to −90°). Of the remaining 3 episodes of nonsustained VT 2 had left-axis deviation (≤-30° to −90°) and 1 had normal QRS axis (>−30° to +90°). Eleven episodes showed right bundle branch block conduction pattern. Six (55%) of these had frontal plane axis directed to the upper right quadrant. The remaining 5 episodes of uniform nonsustained VT had a normal frontal plane QRS axis. The average rate of the uniform nonsustained VT was 140 ± 32 beats/min (range 100 to 200). Mean duration was 5.3 ± 2.0 beats (range 3 to 10). Six (30%) episodes showed an irregular rate resembling atrial fibrillation (Figure 1). Four of

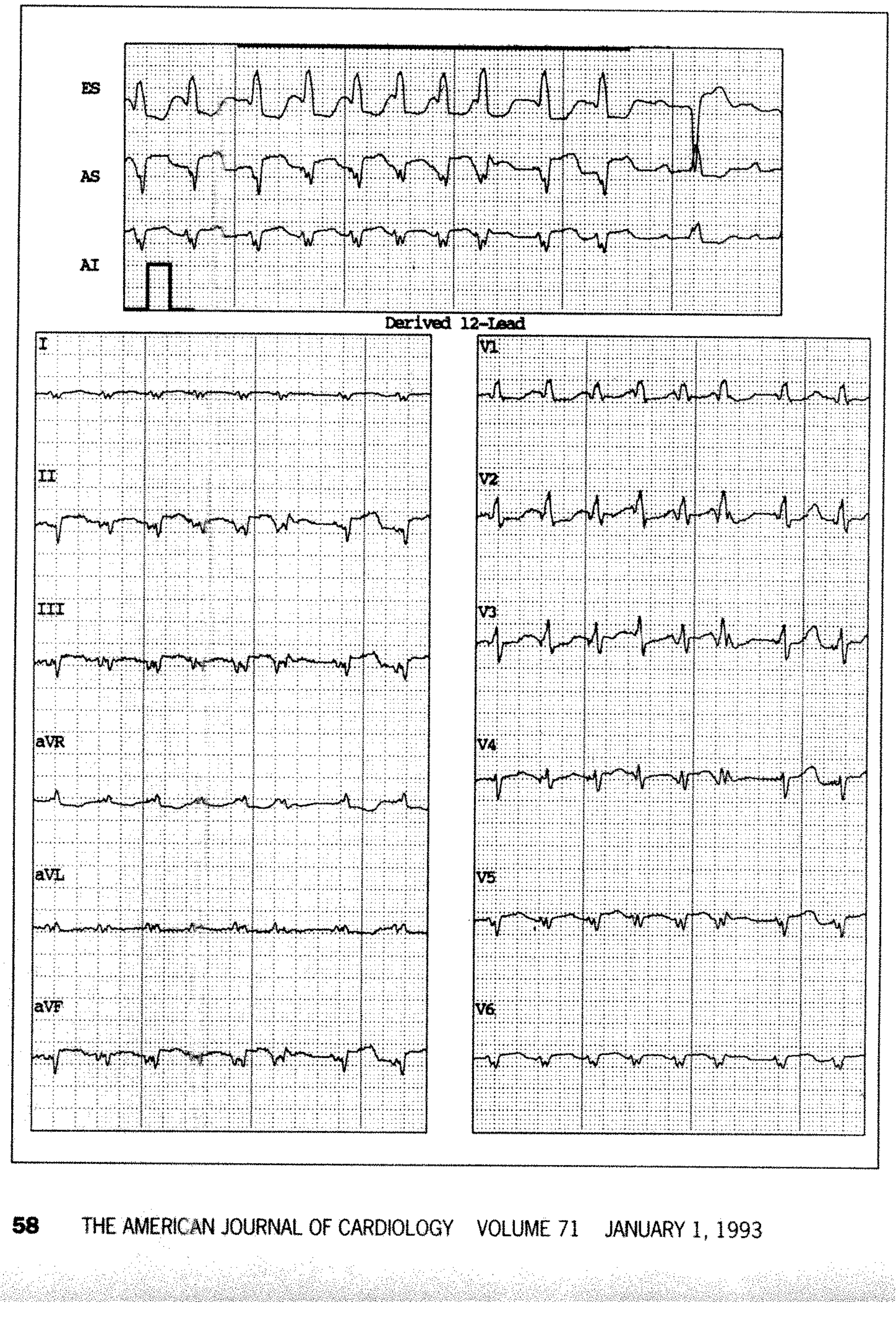

FIGURE 1. Irregular rate of uniform nonsustained ventricular tachycardia. In this and subsequent figures leads ES, AS and AI obtained during Holter recording are shown in the *top panel*. The derived 12-lead electrocardiogram corresponding to the segment of the 3-channel recording marked by the *dark line* is shown in the *bottom panel*. The ventricular tachycardia has right bundle branch block morphology (V_1) with a frontal plane QRS axis directed toward the right upper quadrant (aVR). Note the irregular RR intervals during the tachycardia.

these had rates ≤120 beats/min. Nonsustained VT began with a fusion beat in 2 episodes. There was no R or T initiation seen.

Multiform nonsustained ventricular tachycardia: There were 40 episodes of multiform nonsustained VT. The average rate of multiform nonsustained VT was 124 ± 16 beats/min (range 100 to 160). Mean duration was 4.0 ± 1.0 beats (range 3 to 8). The morphologic features of each QRS complex was examined. Thirty-five of the 40 episodes (87%) had only 2 different QRS morphologic features on the derived 12-lead ECG in each run, irrespective of the duration of the multiform nonsustained VT episode. Four episodes had 3 different QRS configurations and 1 episode had 4 different morphologies. We found 4 unique patterns of QRS morphologies within individual multiform nonsustained VT runs: type I — the QRS of the initial complex has 1 morphology and all subsequent complexes have another configuration (Figure 2). Eight (23%) episodes had this pattern; type II — the initial and the terminal QRS complex of the run has similar configuration (Figure 3). Eighteen (51%) episodes showed this pattern; type III — the initial 2 QRS complexes have similar configuration and all subsequent complexes have another QRS morphology (Figure 4). Two (6%) episodes demonstrated this pattern; type IV — the QRS complexes have alternating QRS morphologies (Figure 5). Four (9%) episodes had this pattern. The remaining 3 episodes did not conform to any of the above-described patterns. One episode was initiated with a ventricular fusion beat. There was no R or T initiation seen.

Multiple nonsustained ventricular tachycardia: Thirteen patients (59%) had multiple nonsustained VT episodes. One patient had only uniform nonsustained VT with 2 different morphologies. Five patients had only multiform nonsustained VT. The number of different QRS morphologies for individual patients varied from 2 to 4 (2 patients had 2 different, 2 had 3 different, and 1 had 4 different morphologies). All patients had ≥2 different patterns of nonsustained VT. Seven patients had both uniform and multiform nonsustained VT. The number of different QRS morphologies for in-

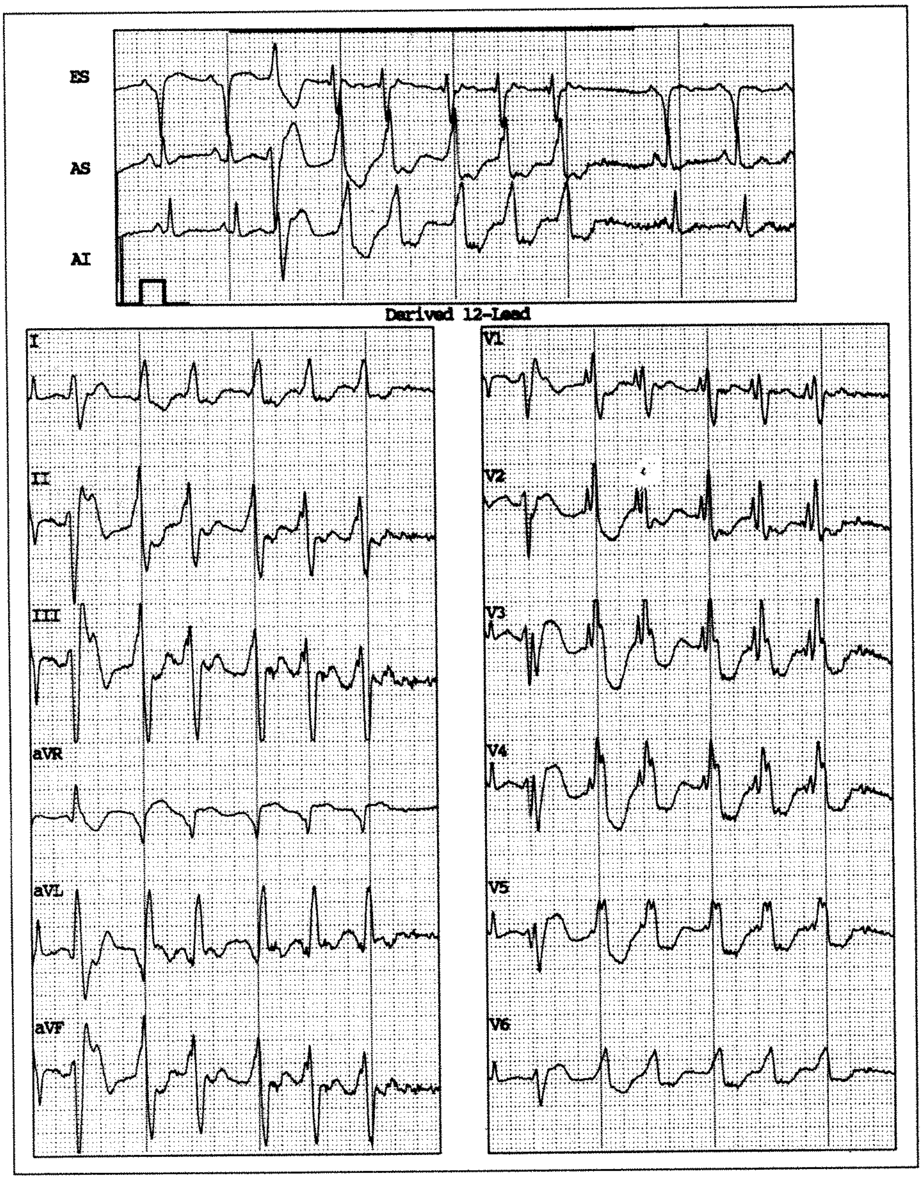

FIGURE 2. Multiform nonsustained ventricular tachycardia, type I pattern. The tachycardia is initiated by a wide QRS complex with a frontal plane axis of -90°; all the subsequent beats of the tachycardia have a different configuration with a frontal plane axis of -30°.

dividual patients varied from 2 to 4 (4 had 2 different, 1 had 3 different and 2 had 4 different morphologies). The QRS morphologies observed during uniform nonsustained VT was not present in any of the multiform episodes in 1 patient; in the remaining 6 patients the QRS morphology during uniform nonsustained VT was also present during the multiform nonsustained VT.

DISCUSSION

Ventricular arrhythmias detected on Holter monitoring are associated with an independent risk for death from cardiac causes.[8] The recently concluded Cardiac Arrhythmia Suppression Trial also demonstrated an association between mortality and nonsustained VT.[2] This clinical trial has shown that successful suppression of nonsustained VT evaluated by Holter monitoring did not result in improved survival.[9] Attempts have been made to use electrophysiologic testing by programmed ventricular stimulation to stratify risk and treat patients with nonsustained VT.[3] Patients who have no inducible sustained VT appear to be at low risk for subsequent arrhythmia events. In contrast, patients with inducible sustained VT have a significantly increased risk for developing an arrhythmic event.[10]

Despite the heightened interest in the evaluation of patients with nonsustained VT, there is only limited information on the morphologic characteristic of this arrhythmia. Dower and Machado[6] described a 3-lead electrocardiographic recording system that can be applied to Holter monitoring. A subsequent report by Dower et al[7] suggested a good correlation between the derived 12-lead ECG_D and the conventional ECGs in a limited number of cases studied. In a recent report, Drew et al[1] demonstrated an excellent correlation between the ECG_D and conventional 12-lead ECG in adults with wide QRS complex tachycardia induced during electrophysiologic testing.

In this report we examined the morphologic features of nonsustained VT in 22 patients by obtaining an ECG_D from patients undergoing 24-hour Holter monitoring with a 3-lead recording system. Our results indicate that in patients with nonsustained VT and coronary artery

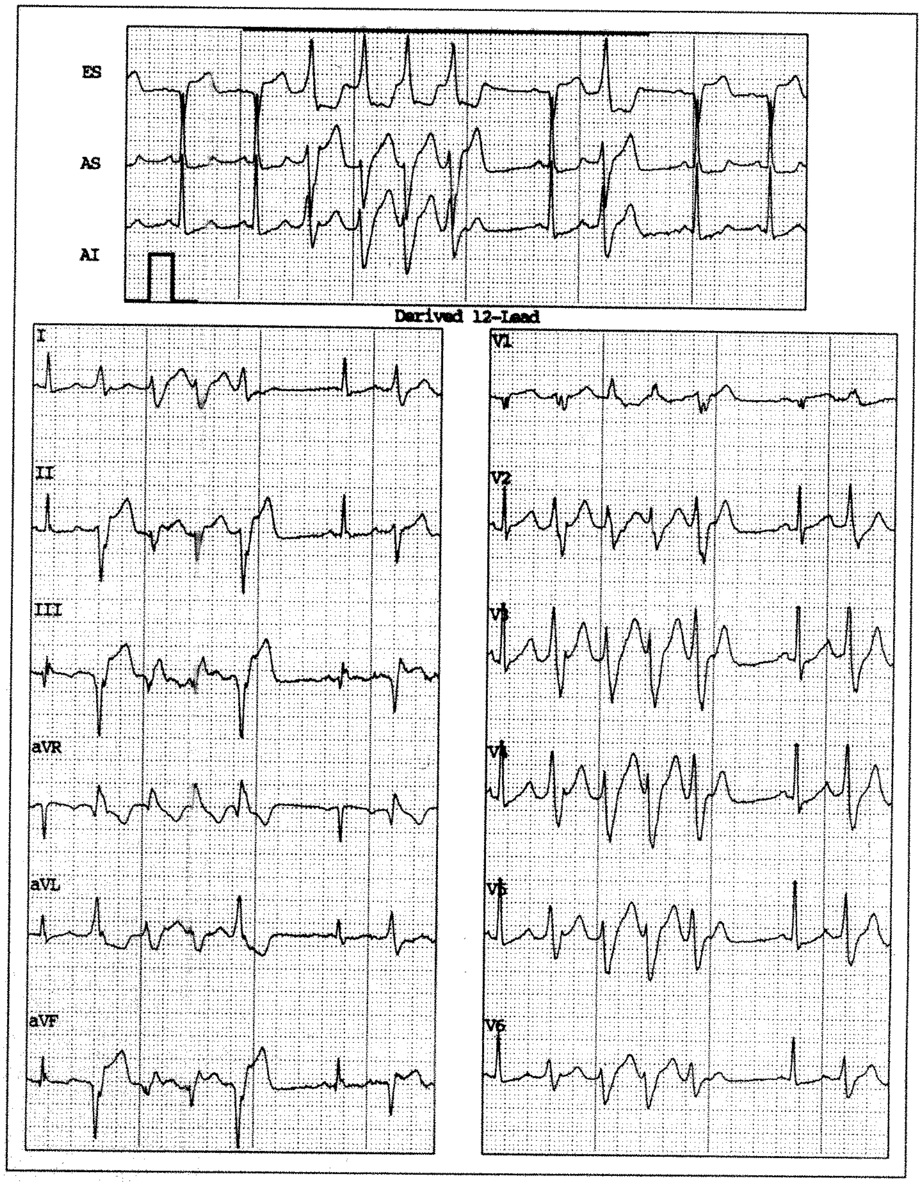

FIGURE 3. Multiform nonsustained ventricular tachycardia, type II pattern. The initial and terminal QRS complex of the tachycardia has similar configuration (left bundle branch block in V_1). In addition, the 3-channel recording erroneously suggests that the tachycardia is uniform. The derived 12-lead electrocardiogram shows the presence of 2 different morphologies (left and right bundle branch block in V_1).

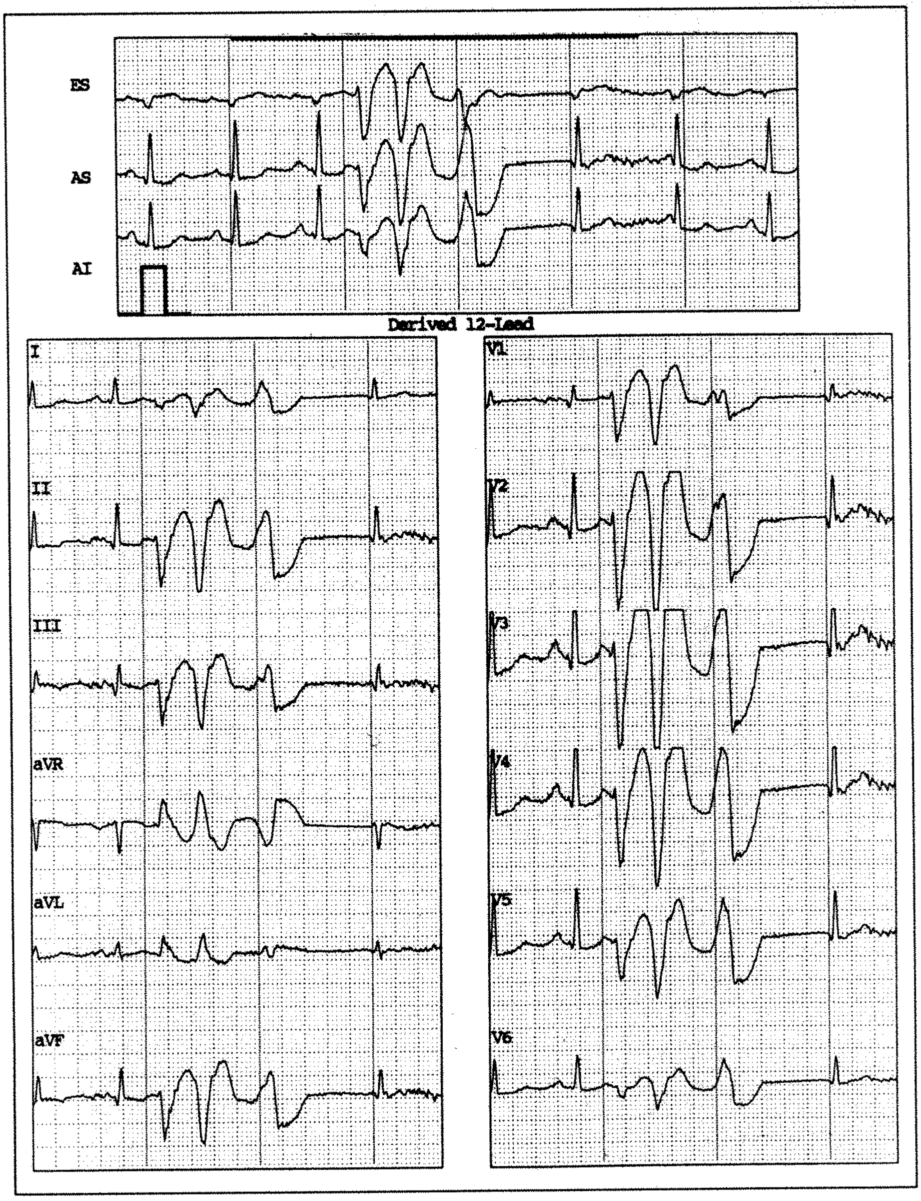

FIGURE 4. Nonsustained ventricular tachycardia, type III pattern. The initial 2 QRS complexes have similar morphology (left bundle branch block in V_1) and the subsequent QRS complex has a different morphology (right bundle branch block in V_1).

disease, multiform episodes appear to be more frequent than uniform nonsustained VT. Multiform episodes are shorter in duration and slower in rate than the uniform runs. Uniform nonsustained VT can show marked variation in RR intervals resembling atrial fibrillation (Figure 1). Most multiform nonsustained VT runs have only 2 different QRS morphologies within the episode. We identified 4 distinct patterns of QRS morphologies within individual multiform nonsustained VT runs. Most (87%) nonsustained VT runs were represented by 1 of these 4 patterns (Figures 2 to 5). The explanation or clinical significance for these patterns is unclear. Type I and III patterns may relate to a reentrant mechanism, whereas patterns II and IV may be explained by the existence of 2 separate foci with automatic firing.

In patients with sustained VT the morphology and rate of the spontaneously occurring episode was compared with VT induced by programmed stimulation, and the induced VT was noted to have a configuration and rate similar to the spontaneously occurring tachycardia.[11] Our study shows that most patients had ≥2 episodes of nonsustained VT, and the morphology and pattern of these episodes frequently varies. It is suggested that the induced nonsustained VT be compared with the spontaneously documented nonsustained VT by examining its morphologic characteristics using the ECG_D recording.

REFERENCES

1. Drew BJ, Scheinman MM, Evans GT Jr. Comparison of a vectorcardiographically derived 12-lead electrocardiogram during wide QRS complex tachycardia, and its potential application for continuous bedside monitoring. *Am J Cardiol* 1992;69:612–618.
2. Denes P, Gillis AM, Pawitan Y, Kammerling JM, Wilhelmsen L, Salerno DM, and the CAST Investigators. Prevalence, characteristics and significance of ventricular premature complexes and ventricular tachycardia detected by 24-hour continuous electrocardiographic recording in the Cardiac Arrhythmia Suppression Trial. *Am J Cardiol* 1991;68:887–896.
3. Kowey PR, Taylor JE, Marinchak RA, Rials SJ. Does programmed stimulation really help in the evaluation of patients with nonsustained ventricular tachycardia? Results of a meta-analysis. *Am Heart J* 1992;123:481–485.
4. Fisch C, DeSanctis RW, Dodge HT, Reeves TJ, Weinberg SL. Guidelines for ambulatory electrocardiography: a report of the American College of Cardiology/American Heart Association Task Force on assessment of diagnostic and therapeutic cardiovascular procedures (subcommittee on ambulatory electrocardiography). *J Am Coll Cardiol* 1989;13:249–258.
5. Dower GE, Machado HB. XYZ data interpreted by a 12 lead computer program using the derived electrocardiogram. *J Electrocardiol* 1979;12:249–261.

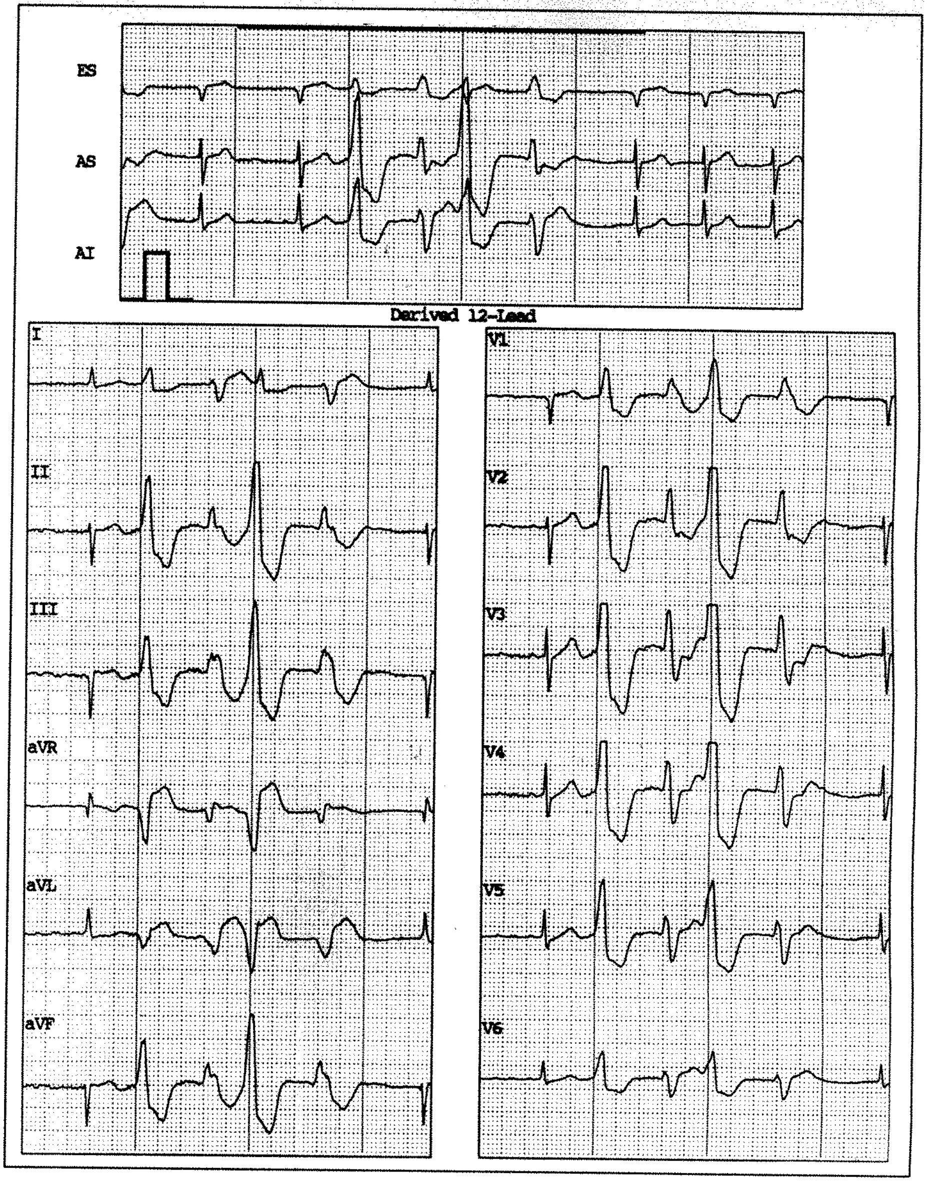

FIGURE 5. Nonsustained ventricular tachycardia, type IV pattern. The QRS complexes have alternating morphology. The first and third QRS complexes have a frontal plane axis of +70°, and the second and fourth complexes have a +110° axis.

6. Dower GE, Machado HB. On deriving the electrocardiogram from vectorcardiographic leads. *Clin Cardiol* 1980;3:87–95.

7. Dower GE, Yakush A, Nazzal SB, Jutzy RV, Ruiz CE. Deriving the 12 lead electrocardiogram from four (EASI) electrodes. *J Electrocardiol* 1988;12:S182–S187.

8. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, and the Multicenter Post-Infarction Group. The relationship between ventricular arrhythmias, left ventricular dysfunction and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250–288.

9. The CAST Investigators Preliminary Report. Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;32:406–412.

10. Wilber DJ, Olshansky B, Moran JF, Scanlon PF. Electrophysiologic testing and nonsustained ventricular tachycardia. Use and limitations in patients with coronary artery disease and impaired ventricular function. *Circulation* 1990;80:350–358.

11. Berger MD, Waxman HL, Buxton AE, Marchlinski FE, Josephson ME. Spontaneous compared with induced onset of sustained ventricular tachycardia. *Circulation* 1988;78:885–892.

Delayed Restoration of Atrial Function After Conversion of Atrial Flutter by Pacing or Electrical Cardioversion

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It is often suggested but never proven that atrial function is not affected during atrial flutter, nor after its conversion to normal sinus rhythm. To evaluate this hypothesis, a prospective study was performed in 22 patients (age range 20 to 88 years) with atrial flutter. Diastolic transmitral flow was analyzed with echo-Doppler before and after conversion. After randomization, conversion was attempted with overdrive pacing or up to two 50 J shocks. If the initial method was unsuccessful, a 200 J shock was administered. All patients were converted to sinus rhythm with this protocol. Shortly after conversion (at 1 and 6 hours), atrial contribution to ventricular filling was absent in 4 of 22 patients. In the remaining 18 patients, atrial contribution to ventricular filling was small. Atrial contribution to transmitral flow improved from 20 to 27% within 24 hours (p <0.01) and increased further to 38% at 6 weeks (p <0.005). Peak velocity of late diastolic filling increased from 0.28 m/s after 1 hour to 0.39 m/s after 24 hours (p <0.0001) and improved even further during later follow-up. In 1 patient, an effective atrial systole was not observed until the 14th day. Cardiac output did not change significantly during the study period. No differences were observed between the conversion modalities. In conclusion, atrial dysfunction is present immediately after conversion of atrial flutter to normal sinus rhythm. This dysfunction occurs also after overdrive pacing and can last >1 week. The findings suggest that stasis in the atria can remain temporarily present after successful conversion of atrial flutter to sinus rhythm.

(Am J Cardiol 1993;71:63–67)

Atrial flutter is a frequently observed arrhythmia, often changing to atrial fibrillation and vice versa.[1-3] Physicians tend to consider flutter as less severe than atrial fibrillation, although atrial flutter and ectopic atrial tachycardia are less well tolerated[4] (e.g., the risk for fast conduction over the atrioventricular node is greater in atrial flutter).[5] For atrial flutter, no data are available concerning the risk for thromboembolism; however, published studies report that patients should not receive antithrombotic therapy.[6,7] Atrial function after conversion of atrial fibrillation remains impaired for a short duration, and immediate return of atrial mechanical function has been associated with emboli.[8,9] Therefore, we assessed atrial function after conversion of atrial flutter by pacing or electrical cardioversion.[1,10,11] A secondary goal of the study was to evaluate possible differences in this respect between overdrive pacing and electrical cardioversion.

METHODS

Patients: A group of 22 patients (mean age 63 ± 14 years) with atrial flutter lasting for >24 hours despite treatment with digoxin was studied after giving informed consent. Patient data are listed in Table I. The mean duration of flutter was 25 ± 46 days. The common (or typical) form of flutter was present in 19 patients, whereas other types were present in the remaining 3. Various etiologies were present, including valvular disease in 5 patients, and other forms of cardiac disease in 8 (hypertensive heart disease in 3, and coronary artery disease in 5). Alcohol abuse was related to the arrhythmia in 2 patients, chronic obstructive pulmonary disease in 2, pneumonia in 1, metastatic pleuritis in 1, and thyroid disorder in 2. Idiopathic flutter was diagnosed in 1 case. All patients were symptomatic. Only 3 patients were in New York Heart Association functional class I. All patients were treated with digoxin, and 11 had received other antiarrhythmic drugs for the present episode of flutter, including amiodarone in 7 cases. The mean ventricular rate at the time of study entry was 126 ± 44 beats/min.

Echocardiography: After the baseline echocardiographic (M-mode and Doppler) study before conversion, the Doppler examination was repeated at 1, 6 and 24 hours, and at 2 and 6 weeks after conversion. The echocardiographic study was performed using a Vingmed CFM 750 instrument (Horten, Norway) with a 2-dimensionally guided, pulsed Doppler module. The initial evaluation included both a 2-dimensionally guided M-

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TABLE I Patient Characteristics and Clinical Data

No. of pts.	22
Men/women	18/4
Age range (year)	20–88
Type I flutter	19
Duration of flutter (days)	3–180
Heart rate (beats/min)	57–207
New York Heart Association functional classification	
II	10
III	9
Etiology	
Valvular disease	5
Other cardiovascular disease	8
General disease	8
Normal	1
Left atrial dimension (mm)	35–57
Fractional shortening (%)	8–45

mode study and a transmitral Doppler flow study. Using the parasternal, long-axis, 2-dimensional image for guidance, M-mode tracing of the left atrium was obtained to measure the left atrial diameter, using the leading-to-leading edge technique. At the baseline echocardiographic study, the same technique was used to determine end-diastolic and end-systolic internal left ventricular dimensions.[12] Transmitral pulsed Doppler examination was performed from the apical long-axis view.[12] The Doppler sample volume was positioned between the tips of the mitral valve leaflets, ensuring that the angle between the presumed direction of the blood flow and the ultrasound beam was <10 degrees. Maximal velocity and velocity time integral of the atrial diastolic filling phase were calculated from the spectral Doppler tracing when an A wave was identifiable (Figure 1). The percentage of atrial contribution to total diastolic transmitral flow (or atrial filling fraction) was calculated. Finally, we used this transmitral Doppler flow spectrum to determine left ventricular stroke volume and to calculate cardiac output.[13]

Cardioversion: Patients were randomized to electrical cardioversion or overdrive pacing. Conversion was performed in the electrophysiologic laboratory in the morning. Disopyramide was administered intravenously in a dosage of 1.5 mg/kg over 15 minutes. Administration began 25 minutes before general anesthesia (for patients randomized to electrical cardioversion) or overdrive stimulation. The flow chart of the conversion methodology is schematically presented in Figure 2.

If a patient was randomized to electrical cardioversion, general anesthesia was administered with propofol infusion by an anesthesiologist. A synchronized, direct-current shock of 50 J was delivered and repeated if no sinus rhythm was obtained. If the second shock was unsuccessful, a 200 J shock was delivered. For patients randomized to overdrive pacing, local anesthesia was administered with lidocaine in a 1% solution, in the right or left femoral groin, to insert a quadripolar pacing catheter through the femoral vein in the right atrium (preferentially in the atrial appendage). Pacing began at a rate that was 110% of the recorded flutter rate to ensure that capture was present with a rectangular pulse of 2 ms width and a current strength ≤10 mA. When capture was not obtained, the catheter was moved in the right atrium. Pacing was performed at rates of 125% and later at 135% of the flutter rate for 30 to 60 seconds until sinus rhythm became present. If this was unsuccessful, a last attempt was performed at 145% of the flutter rate. If no sinus rhythm became present, a 200 J shock was administered after general anesthesia, as described previously.

One hour after the first dose of disopyramide, an additional intravenous dose of 50 mg was administered

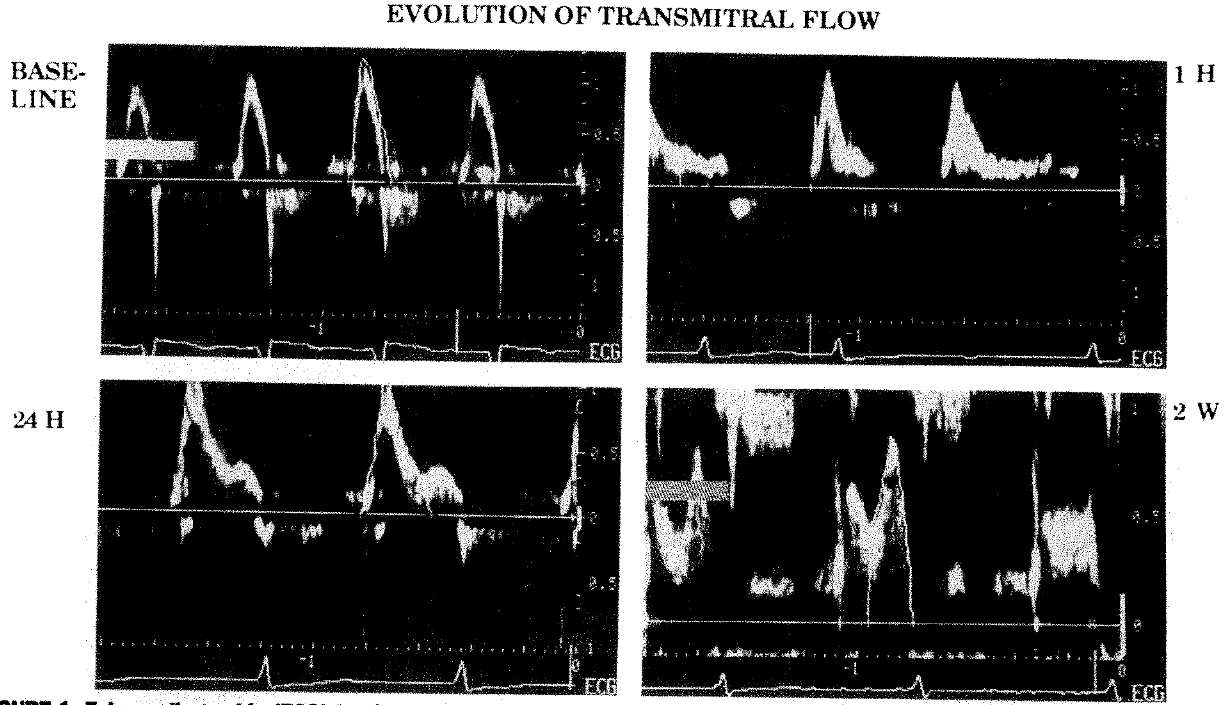

FIGURE 1. Echocardiographic (ECG) tracings obtained in patient 16 at various times during study. Progressively increasing A wave appears after conversion and is very significant at 2 weeks (W). ***Y axis*** **depicts velocity in m/s. H = hours.**

with an oral dose of 250 mg of a long-acting preparation. This was then continued twice daily. Digoxin was continued, and if a patient had side effects of disopyramide, the drug was discontinued.

Clinical follow-up: Clinical examination and electrocardiography to document sinus rhythm were performed at the same intervals as the echocardiographic evaluations.

Statistical methods: Descriptive data are presented as mean and SD of the mean. Ranges are provided in Table I. A nonparametric rank test was used to compare paired data. If data were missing (e.g., echocardiographic values of follow-up period, if atrial fibrillation occurred), only paired data were considered.

RESULTS

Conversion to sinus rhythm: Ten patients were randomized to pacing, and 12 to electrical cardioversion. After infusion of the initial dose of disopyramide, flutter cycle length increased from 206 ± 33 to 254 ± 66 ms ($p < 0.0001$). The cycle length of the ventricular rate decreased from 547 ± 229 to 539 ± 154 ms ($p < 0.05$). All patients achieved sinus rhythm during the procedure without complications.

Of 10 patients treated with pacing, 6 achieved sinus rhythm; of 12 treated with electrical cardioversion, 6 were converted with one 50 J shock, and 1 with two 50 J shocks. Of 9 patients with an unsuccessful initial treatment, 8 were converted with 200 J, and 1 with a 50 J shock.

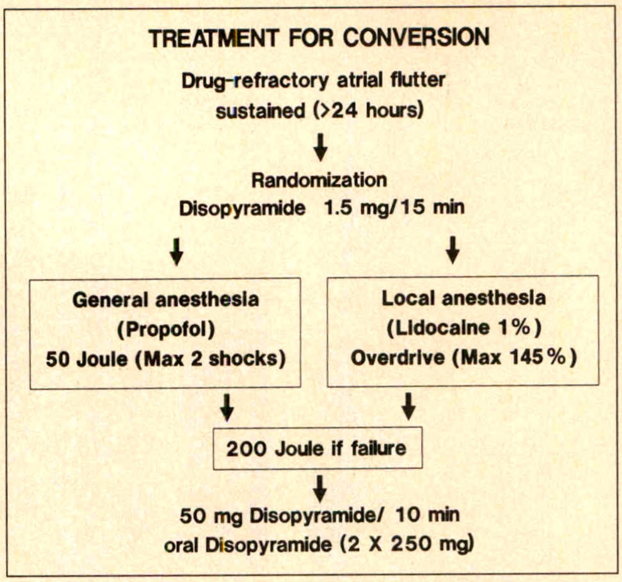

FIGURE 2. General outline of approach for conversion to sinus rhythm.

Hemodynamic assessment: At baseline, mean left atrial diameter measured 45 ± 7 mm, and mean fractional shortening was 27 ± 10%. Cardiac output did not change immediately after conversion (7.2 ± 2.4 liters/min before cardioversion vs 6.8 ± 1.8 after). After 24 hours, the average value remained the same. This was also true when the 24-hour value (7.3 ± 1.4 liters/min) was compared with the last follow-up value (7.3 ± 1.9) for the 15 patients with complete data.

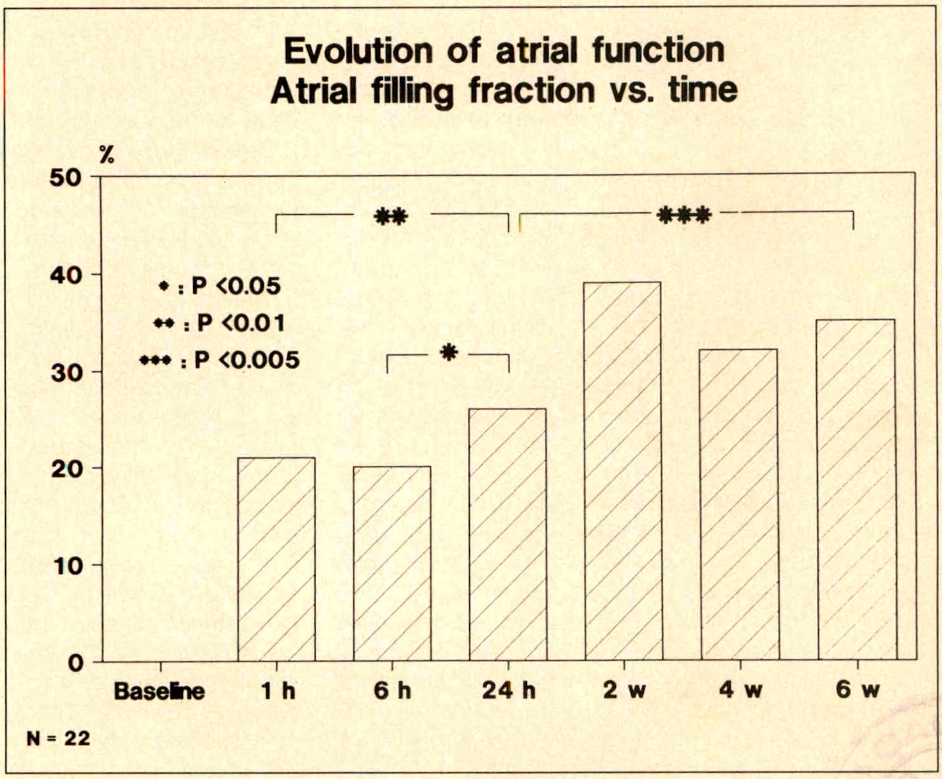

FIGURE 3. Evolution of percent atrial contribution to total transmitral flow (atrial filling fraction) versus time after conversion. h = hours; w = weeks.

The evolution of the atrial filling fraction is shown in Figure 3, and improved from 20 ± 14% to 27 ± 14% within 24 hours ($p < 0.005$) and increased further to 38 ± 16% at 6 weeks ($p < 0.005$). Peak velocity of the atrial diastolic filling phase increased from 0.28 ± 0.16 m/s after 1 hour to 0.39 ± 0.18 after 24 hours ($p < 0.0001$) and improved further to 0.54 ± 0.20 after 6 weeks (Figure 4). In 4 patients, atrial standstill was present after 6 hours and in 2 patients after 24 hours. An effective atri-

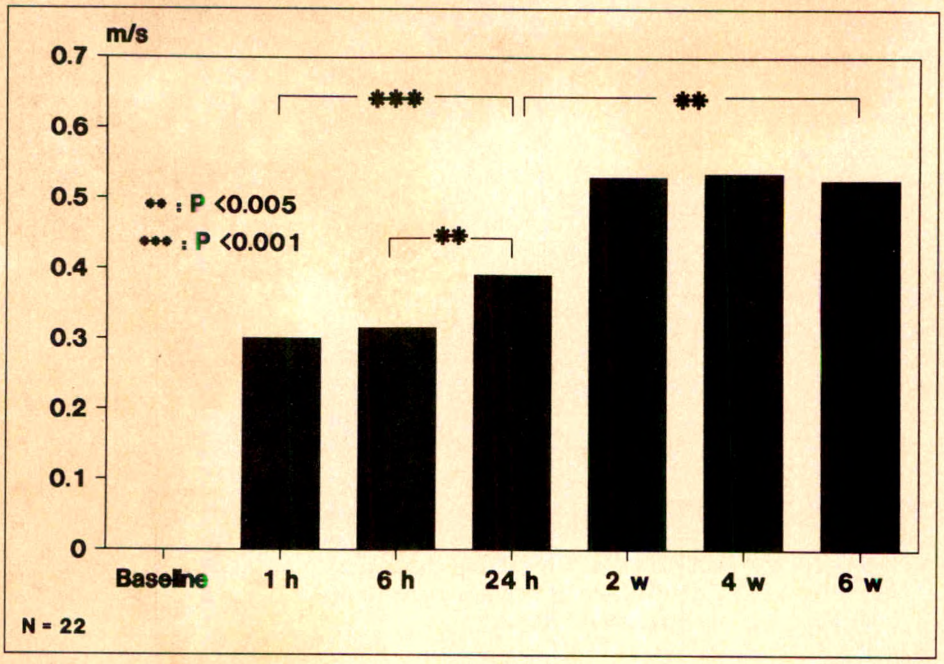

FIGURE 4. Evolution of maximal velocity of early diastolic filling versus time after conversion. h = hours; w = weeks.

TABLE II Hemodynamic Data After Conversion to Sinus Rhythm

		Maximal Velocity (cm/s)				Atrial Filling Fraction (%)				Cardiac Output (liters/min)			
Method	No.	1h	6h	24h	6w	1h	6h	24h	6w	Baseline	1h	6h	24h
Overdrive pacing	6	33	32	40	55	28	25	31	42	8.0	7.1	7.8	7.0
50 J shock	8	26	28	39*	(57)	17	19	25	(37)	7.8	7.1	7.5	8.8
200 J shock	8	25	27	40*	(50)	19	24	27	(23)	7.1	6.2	6.4	7.3

*Statistically significant versus value at 1 hour ($p < 0.05$).
Values in parentheses indicate missing data, because of recurrences before sixth week.
h = hours; w = weeks after conversion.

al systole was only observed for the first time after 14 days. No changes in the diameter of the left atrium were observed between preconversion and at 6 weeks (46 ± 7 vs 43 ± 7 mm).

Differences between conversion methods: No differences were observed for peak velocity and atrial filling fraction between patients treated with overdrive pacing, the protocol with 50 J, or the rescue protocol with high-energy shocks (Table II). Atrial filling fraction did not change over time within 24 hours in the 3 groups. However, peak velocity increased after a shock was administered (both types). The same tendency was observed in the group with pacing without reaching significance.

Clinical follow-up: Recurrences of an atrial arrhythmia occurred in 3 patients during the 6 weeks of the study (at days 2, 9 and 11, respectively). These patients did not have all echocardiographic follow-up data after 24 hours. One of these patients was converted again with amiodarone and overdrive pacing. Definite proarrhythmic effects on disopyramide were observed twice. One patient with valvular and coronary artery disease developed torsades de pointes after 35 days; disopyramide treatment was discontinued, and ventricular pacing was begun for 48 hours. The other patient, an 88-year-old man with chronic obstructive pulmonary disease, died suddenly 1 week after hospital discharge.

DISCUSSION

Atrial contribution to diastolic ventricular filling and hence cardiac output is important, especially in patients with cardiac disease.[14] Atrial arrhythmias with loss of atrial function are deleterious for the myocardium in the long-term, because dilatation of the ventricles occurs.[14,15] Atrial flutter can be particularly disabling, because it has the potential of 1:1 conduction, causing high ventricular rates, and is often associated with coexisting cardiac disease.[5,16,17] Pharmacologic therapy of atrial flutter is disappointing, even with new and very potent antiarrhythmic drugs.[18,19] In contrast, electrical therapy of atrial flutter is very effective.[11,20] Electrical cardioversion with direct-current countershocks is followed by a period of atrial dysfunction.[8,9,21] Whether this temporary atrial "paralysis" or "stunning" is due to the arrhythmia itself or the countershock is not known. However, this may be an indication to begin with the lowest possible energy level or to use other conversion methods, such as overdrive pacing. This appears to be very effective, at least for the common type of atrial flutter.[1,10,17,20]

In this randomized study with both forms of electrical therapy, neither treatment modality proved to be universally effective (at least not when a low shock level of 50 J was selected). This was despite pretreatment with disopyramide, which has been shown to improve the success rate of overdrive pacing.[22] The data on functional impairment in this study are in agreement with previous observations in patients with atrial fibrillation treated with cardioversion (on average with high energy levels).[21,23] We could not demonstrate any difference between the various treatment groups.

Therefore, we conclude that atrial flutter is associated with functional impairment of the atrial myocardium. This can remain present for several days after conversion to sinus rhythm and is not influenced by the conversion methodology. Furthermore, antiarrhythmic therapy to prevent recurrence may be necessary, particularly in the early period after conversion. However, all antiarrhythmic drugs have a negative inotropic effect, and part of the reduced function may be due to the use of disopyramide or to the general anesthesia in the subgroup that underwent cardioversion.

One could question whether some trials on anticoagulation in atrial fibrillation did not include patients with flutter as well. The criteria for fibrillation were well-defined in some studies, and flutter was probably excluded.[24] However, fibrillation was poorly defined in other trials. Recommendations concerning anticoagulation can not be extrapolated to atrial flutter using the data presented in this study, but in regard to hemodynamics, the findings suggest that flutter has the same consequences as fibrillation. Therefore, whether patients with atrial flutter should receive anticoagulation needs to be critically investigated.[25]

REFERENCES

1. Watson RM, Josephson M. Atrial flutter. Electrophysiologic substrates and modes of initiation and termination. *Am J Cardiol* 1980;45:732–741.

2. Olshansky B, Okumura K, Henthorn RW, Waldo AL. Characterization of double potentials in human atrial flutter: studies during transient entrainment. *J Am Coll Cardiol* 1990;15:833–841.

3. Pritchett ELC, Wilkinson WE. New drug application strategies for supraventricular arrhythmias. *Clin Pharmacol Ther* 1991;49:481–487.

4. Kerr CR, Gallagher JJ, Smith WM, Sterba R, German LD, Cook L, Kasell JH. The induction of atrial flutter and fibrillation and the termination of atrial flutter by pacing. *PACE* 1983;6:60–72.

5. Garson A, Bink-Boelkens M, Hoslein P, Hordof AJ, Keane JF, Neches WH, Porter CJ, and the other investigators of the Pediatric Electrophysiology Society. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol* 1985;6:871–878.

6. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;17:622–626.

7. Dunn M, Alexander J, de Silva R, Hildner F. Antithrombotic therapy in atrial fibrillation. *Chest* 1986;89:69S–74S.

8. Shapiro EP, Effron MB, Lima S, Ouyang P, Siu CO, Bush D. Transient atrial dysfunction after conversion of chronic atrial fibrillation to sinus rhythm. *Am J Cardiol* 1988;62:1202–1207.

9. O'Neill PG, Puleo PR, Bolli R, Rokey R. Return of atrial mechanical function following electrical conversion of atrial dysrhythmias. *Am Heart J* 1990;120:353–359.

10. Waldo AL, Maclean WAH, Karp RB, Kouchoukos NT, James TN. Entrainment and interruption of atrial flutter with atrial pacing. *Circulation* 1977;56:737–745.

11. Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias. *JAMA* 1962;182:150–155.

12. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, Sahn DJ, Schiller NB, Tajik A, Teichholz LE, Weyman AE. Report of the American Society of Echocardiography Committee on nomenclature and standards in two- dimensional echocardiography. *Circulation* 1980;62:212–217.

13. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation* 1984;70:425–431.

14. Mitchell JH, Shapiro W. Atrial function and the hemodynamic consequences of atrial fibrillation in man. *Am J Cardiol* 1969;23:556–567.

15. Gilette PC, Wampler DG, Garson A, Zinner A, Ott D, Cooley D. Treatment of atrial automatic tachycardia by ablation procedures. *J Am Coll Cardiol* 1985; 6:405–409.

16. Gallagher JJ. Tachycardia and cardiomyopathy: the chicken-egg dilemma revisited. *J Am Coll Cardiol* 1985;6:1172–1173.

17. Alessie MA, Bonke FIM. Atrial arrhythmias: basic concepts. In: Mandel WJ, ed. Cardiac Arrhythmias. Their Mechanisms, Diagnosis, Management. Philadelphia: Lippincott, 1980:186–207.

18. Hellestrand KJ. Intravenous flecainide acetate for supraventricular tachycardias. *Am J Cardiol* 1988;62:16D–22D.

19. Sihm I, Hansen A, Rasmussen J, Pedersen AK, Thygesen K. Flecainide acetate in atrial flutter and fibrillation. *Eur Heart J* 1990;11:145–148.

20. Greenberg ML, Kelly TA, Lerman BB, DiMarco JP. Atrial pacing for conversion of atrial flutter. *Am J Cardiol* 1986;58:95–99.

21. Manning WJ, Leeman DE, Gotch PJ, Come PC. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. *J Am Coll Cardiol* 1989;13:617–623.

22. Camm AJ, Ward D, Spurrell R. Response of atrial flutter to overdrive atrial pacing and intravenous disopyramide phosphate singly and in combination. *Br Heart J* 1980;44:240–247.

23. Dethy M, Charsat C, Roy D, Mercier LA. Doppler echocardiographic predictors of recurrence of atrial fibrillation after cardioversion. *Am J Cardiol* 1988;62:723–726.

24. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505–1511.

25. Black IW, Hopkins AP, Lee LC, Walsh WF. Thromboembolic risk of atrial flutter (abstr). *J Am Coll Cardiol* 1992;314A.

Use of Multiple Patches During Implantation of Epicardial Defibrillator Systems

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During implantation of epicardial automatic defibrillator systems, occasional patients have difficulty in obtaining adequate defibrillation thresholds. Of 236 consecutive patients undergoing implantation of epicardial defibrillator systems, 18 patients received a 3-patch (n = 15) or 4-patch (n = 3) defibrillator system. Twelve patients who received a multiple-patch defibrillator system had a best 2-patch defibrillation energy requirement of ≥30 J; in the remaining 6 patients less stringent clinical criteria were used in the decision to add a third defibrillator patch (defibrillation energy requirement >18 J in 4 patients, and >20 J in 2 patients). Technically, multiple-patch systems were made possible with either the use of Y-connectors or defibrillators allowing output to 3 patches. In 3 patients, addition of a third epicardial patch still resulted in a defibrillation energy requirement of ≥30 J; in these 3 patients, addition of a fourth patch resulted in a defibrillation energy requirement of ≤20 J. All patients receiving a multiple-patch defibrillator system had a reduction in defibrillation energy requirement, and 12 patients had a reduction in defibrillation energy requirement of ≥10 J over the best 2-patch defibrillation energy requirement. In the patients who eventually had placement of a multiple-patch system, the best 2-patch defibrillation energy requirement was >18 J in 4 patients, >20 J in 2 patients, ≥30 J in 9 patients, and >40 J in 3 patients. After placement of a multiple-patch system, the defibrillation energy requirement was ≤24 J in 1 patient, ≤20 J in 5 patients, ≤18 J in 8 patients, ≤15 J in 2 patients, and ≤10 J in 2 patients. This improvement was significant (p <0.005). During implantable defibrillator placement associated with a high defibrillation energy requirement with a 2-patch system, placement of a 3- or 4-patch system may result in a marked improvement in defibrillation energy requirement.

(Am J Cardiol 1993;71:68–71)

Completely reliable defibrillation is necessary for the effective function of implantable cardioverters-defibrillators. Whereas in most patients acceptable defibrillation energy requirements can be achieved, occasional patients have difficulty in this regard.[1–3] Strategies for improving defibrillation energy requirements include manipulation of patch position, reversal of patch polarity,[4,5] optimization of patch size,[6,7] use of biphasic versus single pulses,[8–12] and use of simultaneous versus sequential shocks.[13–18] However, not all of these techniques are currently commercially available, and some implantations are still characterized by high defibrillation energy requirements.[1–3] Repeated induction of ventricular fibrillation may also potentially increase morbidity in selected cases, and it may be desirable to keep inductions of ventricular fibrillation to a minimum. In this report, we describe the use of multiple (3 or 4) patches during implantation of epicardial defibrillator systems. Each patient had a high defibrillation energy requirement with a 2-patch system, but had a clinically important reduction in defibrillation energy requirement with the subsequent implantation of 1 or 2 additional patches.

METHODS

The patient population consisted of 18 out of 236 consecutive subjects undergoing implantation of a cardioverter-defibrillator with an open-chest, epicardial system. Implantation was achieved with a median sternotomy in 16 patients, a combined left and right lateral thoracotomy in 1 patient, and a combined left and right lateral thoracotomy plus subxyphoid approach in 1 patient. In 2 patients, a second operation several days later was needed so that a separate incision and more complete exposure of the heart could be achieved.

Defibrillation energy requirements were determined with the CPI model 2806 External Cardioverter-Defibrillator (Cardiac Pacemakers, Inc., St. Paul, Minnesota) or the Medtronic model 5355 External Tachyarrhythmia Control Device (Medtronic, Inc., Minneapolis, Minnesota). The defibrillation energy requirement was considered to be the lowest energy level, achieving ≥2 successful defibrillations without a failure. Defibrillation energy requirement was determined using 5 to 6 J increments or decrements in energy. Ventricular fibrillation was induced with alternating current or rapid pacing. Defibrillation was performed after 10 seconds of ventricular fibrillation.

During epicardial patch placement, a posterior left ventricular patch was the cathode and an anterior right

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ventricular patch was the anode. Attempts at placement of a 2-patch defibrillator system were uniformly with 2 large defibrillator patches (radiographic area 38 or 55 cm^2). Defibrillation energy requirements of ≤20 J were carefully sought. A mean of 2.4 configurations (range 1 to 8) using 2 patches were tested before the addition of a third epicardial patch. The decision to add a third defibrillator patch was based on a best 2-patch defibrillation energy requirement of ≥30 J in 12 patients. In 6 patients, less stringent clinical criteria were used. In these 6 patients, defibrillation energy requirements were >18 J in 4 patients and >20 J in 2 patients.

In 3 patients, defibrillation energy requirements were still ≥30 J after placement of a third epicardial patch. In these 3 patients, addition of a fourth epicardial patch resulted in a substantial reduction in defibrillation energy requirement. Multiple-patch systems were made possible with the use of Y-connectors (model 6836, Cardiac Pacemakers, Inc.) or defibrillators allowing for outputs to 3 patches (model 7217B, Medtronic, Inc.).

Statistics: For patients undergoing implantation of a multiple-patch system, the best 2-patch defibrillation energy requirements were compared with the final multiple-patch defibrillation energy requirements using a chi-square test. Patients were grouped into 1 of the following defibrillation energy requirements: ≤10 J, ≤15 J, ≤18 J, ≤20 J, ≤24 J, ≤35 J and ≤45 J. The best 2-patch defibrillation was assigned to the lowest defibrillation energy requirement possible from these groups. For example, if it was known that the best 2-patch defibrillation energy requirement was >30 J, then the defibrillation energy requirement was considered to be ≤35 J.

TABLE I Comparison of Best Two-Patch and Multiple-Patch Defibrillation Energy Requirements in 18 Patients

Pt. No.	Best Two-Patch Energy Requirement (J)	Final Multiple-Patch Energy Requirement (J)
1	>24	≤18
2	>40	≤18
3	>34	≤18
4	>18	≤15
5	>18	≤18
6	>40	≤10
7	>20	≤20
8	>30	≤18
9	>30	≤18
10	>18	≤15
11	>18	≤18
12	30	≤10
13	>32	≤24
14	>30	≤20
15	>32	≤18
16	>35	≤20
17	>30	≤20
18	>40	≤20

RESULTS

Clinical characteristics: In these multiple-patch cases, prior cardiac surgery had been performed in 9 of 18 patients (50%). Coronary artery bypass surgery was performed concomitantly with defibrillator implantation in 5 of 18 patients (28%). Antiarrhythmic drugs were

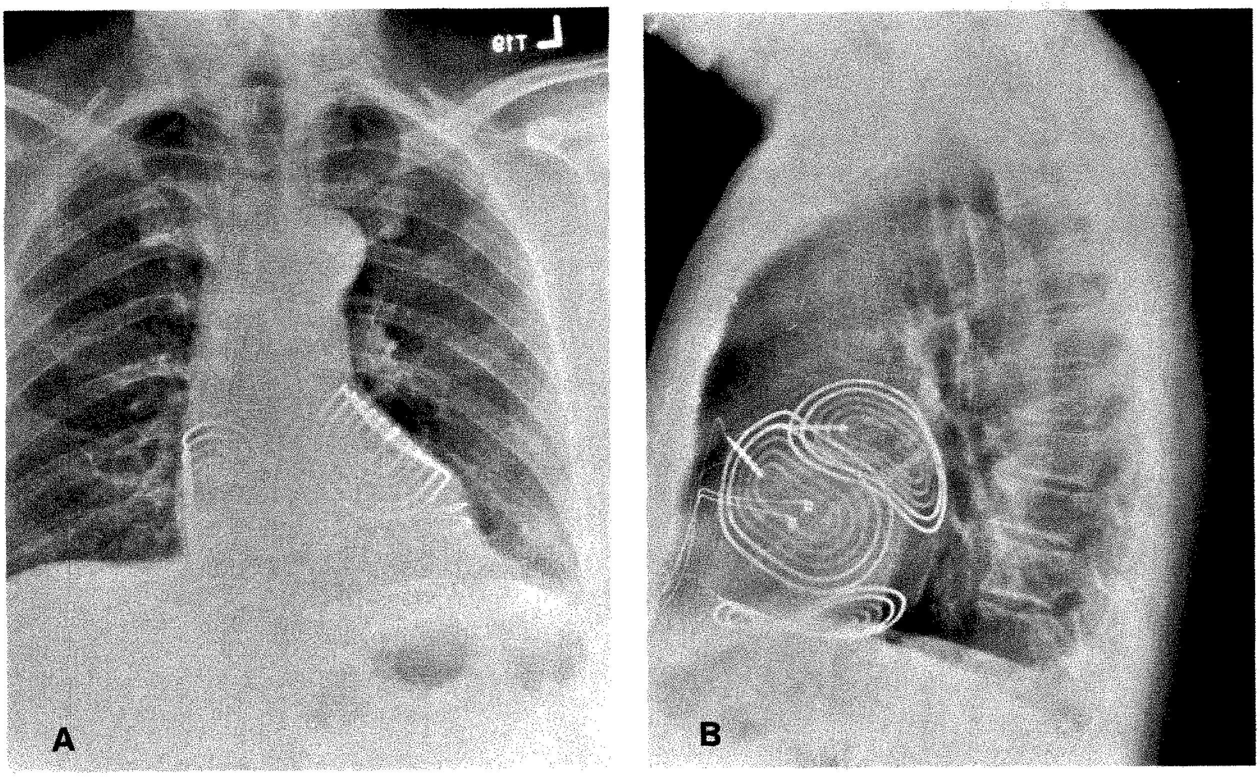

FIGURE 1. ***A and B,* posteroanterior and lateral chest x-rays of a patient with 3 epicardial patches. The cathodal patch is at the posterior left ventricle, and the anodal patches are at the anterolateral left ventricle and the right atrium.**

being administered up to the time of defibrillator implantation in 13 of 18 patients (72%). Left ventricular ejection fraction in this group was 28 ± 14% (range 14 to 54%). The total number of ventricular fibrillation inductions during these multiple-patch cases was 12 ± 5 (range 5 to 20).

Multiple-patch systems: Multiple-patch epicardial defibrillation systems were implanted in 18 patients. Three-patch defibrillator systems were implanted in 15 patients and 4-patch defibrillator systems were implanted in 3 patients. There was improvement in defibrillation energy requirement from the best 2-patch defibrillation energy requirement to the final multiple-patch defibrillation energy requirement in all 18 patients with multiple-patch systems, and this improvement was ≥10 J in 12 of 18 patients (Table I). Before implantation of the multiple-patch system in these 18 patients, the best 2-patch defibrillation energy requirement was >18 J in 4 patients, >20 J in 2 patients, ≥30 J in 9 patients, and >40 J in 3 patients. After implantation of a multiple-patch system, the defibrillation energy requirement was ≤24 J in 1 patient, ≤20 J in 5 patients, ≤18 J in 8 patients, ≤15 J in 2 patients, and ≤10 J in 2 patients. This improvement was significant ($p < 0.005$). When 3-patch systems were used, the cathodal patch was placed at the posterior or posteroapical left ventricle, and the anodal patches were placed at the anterior or anterolateral left ventricle and the anterior right ventricle or right atrium. Four-patch systems used 2 cathodal and 2 anodal patches in 2 cases, and 3 cathodal and 1 anodal patch in 1 case. Examples of patch position as seen by chest x-ray are shown in Figures 1 and 2.

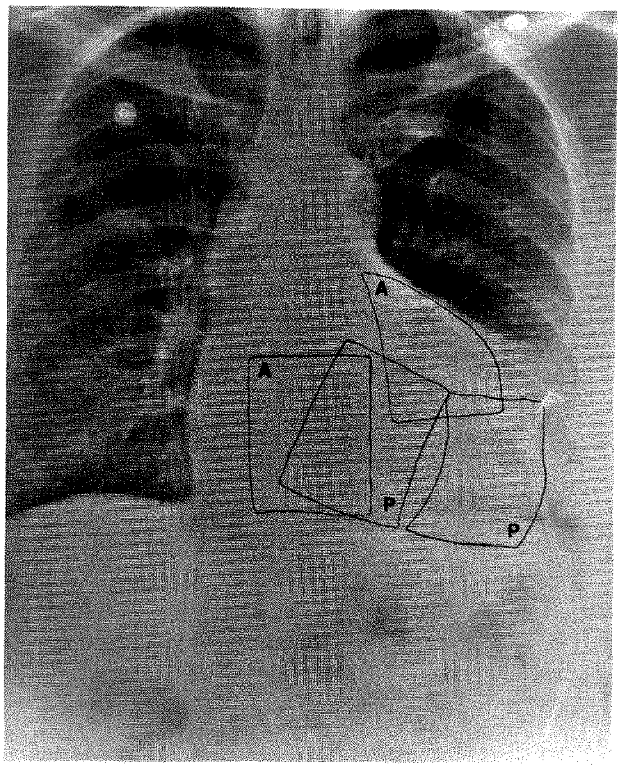

FIGURE 2. Posteroanterior chest x-ray of a patient with 4 epicardial patches. Cathodal patches are side by side at the posterior left ventricle (P), and anodal patches are at the anterior left and right ventricles (A). For clarity, the patch edges have been outlined in *black*.

Simultaneous versus sequential shocks: In patients with multiple-patch defibrillator systems the possibility exists of giving either simultaneous or sequential shocks. Defibrillators capable of giving both simultaneous and sequential shocks were used in 13 of 18 patients, and defibrillators capable of simultaneous shocks only were used in 5 of 18 patients. In 8 patients, the final configuration was for simultaneous shocks. Six of these 8 patients were tested only in the simultaneous configuration, and 2 of the 8 patients had a change from sequential to simultaneous shocks in order to obtain improved defibrillation energy requirements. In 10 patients, the final configuration was for sequential shocks. Nine of the 10 patients were tested only in the sequential configuration, and 1 of the 10 patients had a change from simultaneous to sequential shocks in order to obtain improved defibrillation energy requirements.

Follow-up: Fifteen of the 18 patients with multiple-patch defibrillator systems are alive at a follow-up of 11.4 ± 5.6 months (range 3.5 to 19). One patient died of electrical-mechanical dissociation, 1 patient died of respiratory failure, and 1 patient underwent cardiac transplantation. During this time, none of the patients have developed evidence of constrictive pericarditis.

DISCUSSION

In this study, with the use of a multiple (3 or 4) epicardial patch defibrillator system, substantial improvements in defibrillation energy requirements were obtained in patients having high defibrillation energy requirements with a 2-patch system. The strategy of using multiple defibrillator patches in patients having high defibrillation energy requirements with a 2-patch system may reduce the number of patients with borderline or inadequate defibrillator function. It may also serve to reduce the number of inductions of ventricular fibrillation in cases where initial attempts at a 2-patch epicardial defibrillator system are unsuccessful.

Our study is consistent with the animal study of Montenero et al,[19] in which using both 2- and 3-patch epicardial systems of the same total surface area, the 3-patch systems had significantly lower defibrillation energy requirements. The reduction in defibrillation energy requirements was greatest in animals having the highest defibrillation energy requirements with a 2-patch system. In this clinical study, an increase in the number of patches obviously increased the total surface area of the patches. It is likely that the increase in patch number and total surface area of the patches had additive effects in improving defibrillation energy requirements.

Despite these advantages, there are several potential disadvantages to the application of multiple epicardial defibrillator patches. The application of multiple patches may be more likely to impair ventricular function than 2 patches. Constrictive pericarditis has been reported in association with epicardial patch placement.[20] Although no patient developed symptoms of constrictive pericarditis in 11.4 ± 5.6 months of follow-up, this occurrence should be watched for carefully. Also, although the use of multiple patches may provide superior distribution of current density, if the edges of the anode and cathode are too close, current shunting and possible tissue injury may occur.[21] Furthermore, epicardial patch electrodes have been reported to have deleterious effects on external defibrillation,[22,23] and the use of multiple patches would be expected to exacerbate this problem.

One shortcoming of this study is the retrospective nature of the analysis. Because of this, there were no uniform criteria for the abandonment of attempts at a 2-patch defibrillator system, and placement of a multiple-patch system. However, given the occasional intraoperative hemodynamic instability in patients undergoing implantable defibrillator placement, and given periodic limitations in the maneuvering of epicardial defibrillator patches due to the presence and location of aortocoronary bypass grafts, it is doubtful that uniform criteria for the number of 2-patch defibrillator configurations tested could be rigidly adhered to, even in a prospective study.

In conclusion, in patients experiencing high epicardial defibrillation energy requirements with a 2-patch system, use of a third or fourth patch may dramatically reduce defibrillation energy requirements. With 11.4 ± 5.6 months of follow-up, none of the 18 patients in this series developed adverse consequences from use of the multiple-patch system.

Acknowledgment: We gratefully acknowledge the excellent technical assistance of Karen McDonald, RN, Sally Botkin, RN, and Barbara Sirovatka, RN.

REFERENCES

1. Pinski SL, Vanerio G, Castle LW, Morant VA, Simmons TW, Trohman RG, Wilcoff BL, Maloney JD. Patients with a high defibrillation threshold: clinical characteristics, management, and outcome. *Am Heart J* 1991;122:89–95.

2. Echt DS, Armstrong K, Schmidt P, Oyer PE, Stinson EB, Winkle RA. Clinical experience, complications, and survival in 70 patients with the automatic implantable cardioverter/defibrillator. *Circulation* 1985;71:289–296.

3. Marchlinski FE, Flores B, Miller JM, Gottlieb CD, Hargrove WC. Relation of the intraoperative defibrillation threshold to successful postoperative defibrillation with an automatic implantable cardioverter defibrillator. *Am J Cardiol* 1988;62: 393–398.

4. Bardy GH, Ivey TD, Allen MD, Johnson G, Greene HL. Evaluation of electrode polarity on defibrillation efficacy. *Am J Cardiol* 1989;63:433–437.

5. O'Neill PG, Boahene KA, Lawrie GM, Harvill LF, Pacifico A. The automatic implantable cardioverter-defibrillator: effect of patch polarity on defibrillation threshold. *J Am Coll Cardiol* 1991;17:707–711.

6. Dixon EG, Tang ASL, Wolf PD, Meador JT, Fine MJ, Calfee RV, Ideker RE. Improved defibrillation thresholds with large contoured epicardial electrodes and biphasic waveforms. *Circulation* 1987;76:1176–1184.

7. Kallok MJ, Bourland JD, Tacker WA, Jones DL, Klein GJ, Wessale JL. Optimization of epicardial electrode size and implant site for reduced sequential pulse defibrillation thresholds. *Med Instrumentation* 1986;20:36–39.

8. Kavanagh KM, Tang ASL, Rollins DL, Smith WM, Ideker RE. Comparison of the internal defibrillation thresholds for monophasic and double and single capacitor biphasic waveforms. *J Am Coll Cardiol* 1989;14:1343–1349.

9. Chapman PD, Vetter JW, Souza JJ, Wetherbee JN, Troup PJ. Comparison of monophasic with single and dual capacitor biphasic waveforms for nonthoracotomy canine internal defibrillation. *J Am Coll Cardiol* 1989;14:242–245.

10. Chapman PD, Vetter JW, Souza JJ, Troup PJ, Wetherbee JN, Hoffmann RG. Comparative efficacy of monophasic and biphasic truncated exponential shocks for nonthoracotomy internal defibrillation in dogs. *J Am Coll Cardiol* 1988;12:739–745.

11. Wharton JM, Richard VJ, Murry CE, Dixon EG, Reimer KA, Meador J, Smith WM, Ideker RE. Electrophysiologic effects of monophasic and biphasic stimuli in normal and infarcted dogs. *PACE* 1990;13:1158–1172.

12. Swartz JF, Jones JL, Jones RE, Fletcher R. Conditioning prepulse of biphasic defibrillator waveforms enhances refractoriness to fibrillation wavefronts. *Circ Res* 1991;68:438–449.

13. Bourland JD, Tacker WA, Wessale JL, Kallok MJ, Graf JE, Geddes LA. Sequential pulse defibrillation for implantable defibrillators. *Med Instrumentation* 1986;20:138–142.

14. Jones DL, Klein GJ, Guiraudon GM, Sharma AD, Kallok MJ, Bourland JD, Tacker WA. Internal cardiac defibrillation in man: pronounced improvement with sequential pulse delivery in two different lead orientations. *Circulation* 1986; 73:484–491.

15. Chang MS, Inoue H, Kallok MJ, Zipes DP. Double and triple sequential shocks reduce ventricular defibrillation threshold in dogs with and without myocardial infarction. *J Am Coll Cardiol* 1986;8:1393–1405.

16. Jones DL, Klein GJ, Guiraudon GM, Sharma AD. Sequential pulse defibrillation in humans: orthogonal sequential pulse defibrillation with epicardial electrodes. *J Am Coll Cardiol* 1988;11:590–596.

17. Bardy GH, Ivey TD, Allen MD, Johnson G, Greene HL. Prospective comparison of sequential pulse and single pulse defibrillation with use of two different clinically available systems. *J Am Coll Cardiol* 1989;14:165–171.

18. Jones DL, Sohla A, Bourland JD, Tacker WA, Kallok MJ, Klein GJ. Internal ventricular defibrillation with sequential pulse countershock in pigs: comparison with single pulses and effects of pulse separation. *PACE* 1987;10:497–502.

19. Montenero AS, Bombardieri G, Barilaro C, Di Francesco P, Bertazzoni S, Santarelli P, Pisano E, Alessandrini F, Possati G. Comparison between two versus three patches single pulse shock defibrillation in pigs. *PACE* 1991;14:362–365.

20. Almassi GH, Chapman PD, Troup PJ, Wetherbee JN, Olinger GN. Constrictive pericarditis associated with patch electrodes of the automatic implantable cardioverter-defibrillator. *Chest* 1987;92:369–371.

21. Ideker RE, Wolf PD, Alferness C, Krassowska W, Smith WM. Current concepts for selecting the location, size and shape of defibrillation electrodes. *PACE* 1991;14:227–240.

22. Walls JT, Schuder JC, Curtis JJ, Stephenson HE, McDaniel WC, Flaker GC. Adverse effects of permanent cardiac internal defibrillator patches on external defibrillation. *Am J Cardiol* 1989;64:1144–1147.

23. Lerman BB, Deale OC. Effect of epicardial patch electrodes on transthoracic defibrillation. *Circulation* 1990;81:1409–1414.

Impaired Immediate Vasoconstrictor Responses in Patients with Recurrent Neurally Mediated Syncope

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Immediate responses to head-up tilt were determined in 78 consecutive patients with unexplained syncope undergoing 45-minute tilt tests at 60°. Thirty-four patients developed neurally mediated syncope (mean time to syncope 18 minutes), 40 tolerated the full duration of tilt, and 4 were unable to complete the study but did not develop syncope. Blood pressure, heart rate, forearm blood flow and forearm vascular resistance were measured at baseline and after 2 and 5 minutes of tilt. Syncopal and nonsyncopal patients were well-matched for age and baseline hemodynamic parameters. There was no difference between the groups in heart rate or blood pressure at 2 minutes, but there was a small but significant difference in percent reduction in mean arterial pressure at 5 minutes. After 2 and 5 minutes of tilt, mean forearm blood flow was 2.4 and 2.6 ml/min/100 ml, respectively, in syncopal patients compared with 1.6 ($p < 0.05$) and 1.7 ml/min/100 ml ($p < 0.01$), respectively, in patients who tolerated 45 minutes of tilt. In syncopal patients, forearm vascular resistance was 51.0 and 44.0 at 2 and 5 minutes, respectively, whereas in nonsyncopal patients, it was 82.4 ($p < 0.02$) and 73.1 ($p < 0.001$), respectively. These differences remained consistent when only data for patients developing syncope after >15 minutes were included in the analysis. Patients with neurally mediated syncope have clearly demonstrable abnormalities in vascular control immediately after assumption of the upright posture. The results shed new light on the pathophysiology of neurally mediated syncope.

(Am J Cardiol 1993;71:72–76)

Tilt testing in the investigation of patients with unexplained syncope has been recently recognized as a useful diagnostic technique to identify those with neurally mediated syncope.[1–5] In patients without significant structural heart disease who have an inconclusive history, examination and noninvasive investigation, tilt testing is now recommended as the next diagnostic test before proceeding to invasive electrophysiologic investigation.[1] The major hemodynamic characteristics of vasovagal reactions have been known for many years.[6,7] The original studies showed that the precipitous reduction in blood pressure was largely due to inappropriate vasodilation. The potential for vasovagal reactions is a universal phenomenon, provided that the stimulus is sufficiently strong.[8] Normal subjects with no history of syncope frequently have such reactions, if they are subjected to very prolonged orthostatic stress, particularly if supported on a saddle rather than a footplate. The causes of individual susceptibility to vasovagal reactions in response to modest degrees of stress during everyday life or diagnostic tilt testing remain to be explained. Because one major manifestation of neurally mediated syncope is profound muscle bed vasodilation, this study was designed to examine the initial changes in forearm blood flow during head-up tilt in patients referred for tilt testing for the evaluation of syncope or presyncope.

METHODS

Patients: Seventy-eight consecutive patients (42 men and 36 women, mean age 48.5 ± 21 years, range 11 to 92) with recurrent syncope or presyncope referred for head-up tilt testing constituted the study cohort. All patients previously underwent clinical evaluation, 12-lead electrocardiography, 24-/48-hour Holter monitoring, echocardiography and neurologic evaluation, if appropriate. No patient had diabetes mellitus, clinical evidence of neuropathy, or echocardiographic evidence of significant structural heart disease. Four patients previously underwent permanent VVI pacing that had no impact on the frequency or severity of symptoms. Their pacemakers were programmed to minimal rate and maximal hysteresis before the study. Tilt testing was selected by the referring physicians as the next diagnostic maneuver, because no conclusive cause for the patients' symptoms was revealed by their initial assessment. All cardiac and vasoactive drugs were withdrawn ≥ 5 half lives before the tilt study. Although all tilt tests were performed as part of the patients' clinical investigation, all

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subjects gave informed consent to the additional measurements as part of a protocol approved by this institution's ethics committee.

Tilt protocol: All tilt studies were performed in the morning after an overnight fast. Patients rested supine for 15 minutes in a quiet, temperature-controlled environment (21 to 23°C) and were then tilted head-up to 60° on a tilt table with footplate support. Patients were returned to the supine position if a positive response occurred or after a maximum of 45 minutes of tilt. A positive response was defined as the development of syncope or a reduction in systolic blood pressure to <50 mm Hg with symptoms of presyncope.

Hemodynamic measurements: Heart rate and blood pressure were recorded on a Lectromed chart recorder using a 3-lead electrocardiogram and an Ohmeda Finapress 2300 photoplethysmographic device,[9] respectively. The appropriately sized finger cuff was used, and the hand was supported in a sling so that the cuff was held at the height of the right atrium. Blood pressure in the supine position was corrected to the midaxillary line. Forearm blood flow was measured using intermittent venous occlusion with a temperature-compensating Whitney mercury in silastic strain gauge.[10,11] A cuff at the wrist (to exclude the hand from the circulation) was inflated to 20 mm Hg greater than the systolic pressure from 1 minute before and during measurements. The venous occlusion cuff was inflated to 40 mm Hg during each measurement. The arm was supported on a custom-designed suspended platform so that there was no obstruction to arterial or venous flow. The height of the arm was maintained to keep the gauge at right atrial level in both the supine and tilted positions. The gauge was calibrated in situ on the arm in the supine and tilted positions. Forearm blood flow was calculated from 3 to 5 slopes using techniques described previously.[12] Forearm vascular resistance was calculated as mean arterial pressure divided by forearm blood flow. Hemodynamic measurements were obtained immediately before tilting, after 2, 5 and 10 minutes of tilt, and at 10 minute intervals until the end of the study. Measurements were obtained immediately before and after return of the patient to the supine position.

Statistical analysis: The normality of each data set was examined. Either a paired or unpaired *t* test was used for normally distributed data, and nonparametric tests were used if the data were skewed. Because data at 2 and 5 minutes were included in the study, the Bonferroni correction was applied to the resulting p values, and $p < 0.05$ was considered significant. For subgroup analysis, data were examined using analysis of variance owing to the multiplicity of tests.

RESULTS

Tilt tests: Thirty-four patients (43.6%) had a positive response to head-up tilt (Table I). The mean duration of tilt in these patients was 18 ± 10 minutes (range 0 to 39). Forty patients (51.2%) tolerated the tilt test without symptoms or hypotension, and 4 (5.2%) were unable to complete the study because of arthritis ($n = 3$) or a panic attack ($n = 1$). Two patients developed syncope so early (1 while supine, and 1 after 45 seconds of tilt) that blood flow data could not be obtained, and in 4 (1 tilt-positive, and 3 tilt-negative), blood flow data are not available for technical reasons. Hemodynamic data are presented for the 68 patients who completed the protocol and for whom complete data are available. There was no significant difference in age between the groups who completed the study, although there was a trend toward older age in the tilt-positive group (tilt-positive 50.5 ± 21.0 years vs tilt negative 44.1 ± 20.0; $p = 0.2$). There was a significantly higher rate of positive tests in men. Echocardiographic abnormalities were present in 6 patients with positive tilts; 3 had mild concentric left ventricular hypertrophy, 2 had mitral valve prolapse, and 1 had a hemodynamically insignificant ventricular septal defect. Of patients with negative tilts, 3 had left ventricular hypertrophy and 2 had mitral valve prolapse.

Hemodynamic results: Of 34 patients with tilt-induced syncope, 20 had cardioinhibitory responses with a reduction in heart rate to <60 beats/min, and 14 had predominantly vasodepressor responses. In the tilt syncope group as a whole, at the time of syncope the mean reduction in arterial pressure from baseline was 48 mm Hg ($p < 0.0001$), the mean reduction in heart rate 11.7 beats/min ($p < 0.02$) and the mean reduction in forearm

TABLE I Characteristics of the 74 Patients Who Completed the Study

	Tilt Positive	Tilt Negative	
No. of pts.	34 (46%)	40 (54%)	
Mean age (year)	50.5 ± 21.9	44.1 ± 20.3	p = 0.2
Sex (M/F)	23/11	15/25	p = 0.05
Mean no. of syncopal episodes	4.2 ± 5.1	5.5 ± 9.1	NS
Median no. of syncopal episodes	3.0	2.5	NS

Table includes 4 patients for whom hemodynamic data was not available.

TABLE II Hemodynamic Results After Head-Up Tilt

	Time After Tilt		
	0	2 Minutes	5 Minutes
Mean arterial pressure (mm Hg)			
Positive	95 ± 14	96 ± 15	93 ± 17
Negative	97 ± 13	100 ± 14	100 ± 14
	NS	NS	p = 0.06
Heart rate (beats/min)			
Positive	66 ± 13	81 ± 16	80 ± 15
Negative	69 ± 14	82 ± 17	82 ± 17
	NS	NS	NS
Forearm blood flow (ml/min/100 ml)			
Positive	3.5 ± 1.8	2.4 ± 1.6	2.6 ± 1.6
Negative	3.7 ± 2.0	1.6 ± 0.9	1.7 ± 0.9
	NS	p <0.05	p <0.01
Forearm vascular resistance (arbitrary units)			
Positive	33.9 ± 17.6	51.0 ± 23.6	44.0 ± 20.3
Negative	32.7 ± 14.3	82.4 ± 52.3	73.1 ± 31.6
	NS	p <0.02	p <0.001

vascular resistance 16.5 ($p < 0.0001$). For tilt-negative patients, the mean change in arterial pressure from baseline to 45 minutes of tilt was –0.3 mm Hg ($p = 0.9$), in heart rate +20.4 beats/min ($p < 0.0001$) and in forearm vascular resistance +57.4 ($p < 0.0001$).

Heart rate, mean arterial blood pressure, forearm blood flow and vascular resistance were not significantly different between the groups at baseline (Table II). At 2 minutes of tilt, there was no difference in blood pressure or heart rate nor in the actual and percent changes between the 2 groups. Forearm blood flow and vascular resistance at 2 minutes were significantly different in patients who eventually developed syncope. The percent changes in blood flow and vascular resistance were even more markedly different (Figure 1). At 5 minutes of tilt, there was no difference in heart rate, but even at this early stage, there was a significant but small percent reduction in mean arterial pressure. The differences in forearm blood flow and vascular resistance remained consistent at 5 minutes (Figures 2 and 3). The sensitivity and specificity of percent changes in forearm vascular resistance at 2 and 5 minutes of tilt in predicting subsequent syncope are shown in Figure 4.

DISCUSSION

This study demonstrated impaired early vasoconstrictor responses to head-up tilt in patients who subsequently developed vasovagal reactions considerably later during continued orthostatic stress.

Normal responses to tilt: Assumption of the upright position results in venous pooling in dependent parts and a reduction in central venous pressure. Stroke volume decreases and despite an increase in heart rate, cardiac output decreases approximately 20%.[13] Arterial pressure is maintained by vasoconstriction in both muscle and splanchnic beds. Using lower body negative pressure to simulate gravitational stress, Abboud et al[14] reported that forearm (muscle) flow was largely under cardiopulmonary baroreceptor control, with only a minor contribution from carotid baroreceptors. In contrast, splanchnic flow was mainly modulated by carotid baroreceptors.

The mechanism of vasovagal syncope: Several studies have characterized the hemodynamic events at the time of the vasovagal reaction, but few have examined the immediate responses to tilt in patients susceptible to vasovagal reactions and none have assessed fore-

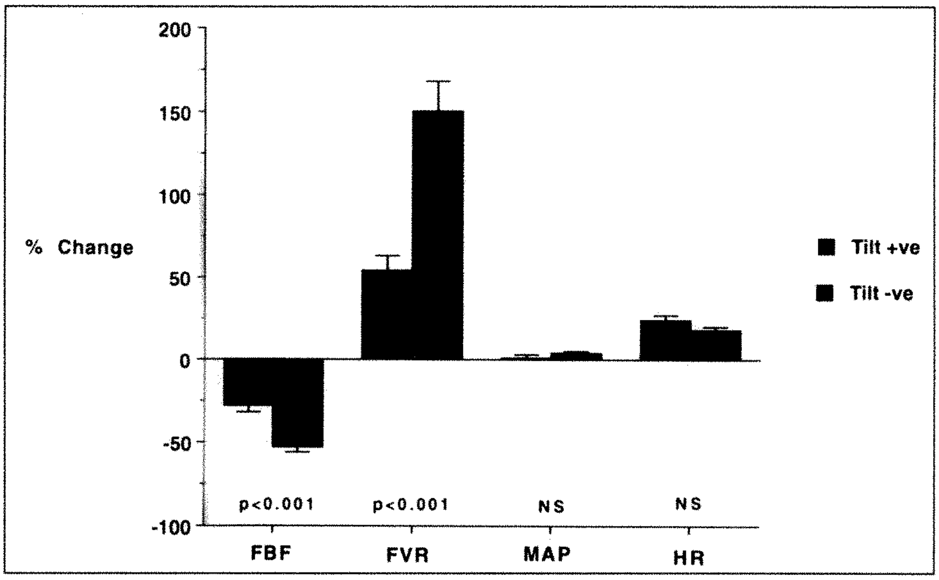


FIGURE 1. Percent changes in forearm blood flow (FBF), forearm vascular resistance (FVR), mean arterial pressure (MAP) and heart rate (HR) after 2 minutes of 60° head-up tilt in patients with tilt-induced neurally mediated syncope (Tilt +ve; n = 31) and in those who tolerated 45 minutes of tilt (Tilt -ve; n = 37).

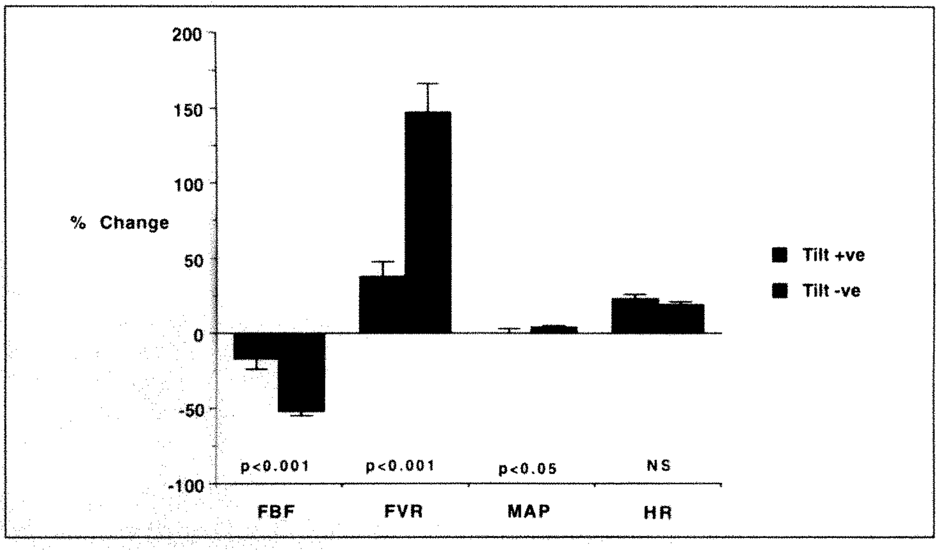


FIGURE 2. Percent changes in forearm blood flow (FBF), forearm vascular resistance (FVR), mean arterial pressure (MAP) and heart rate (HR) after 5 minutes of 60° head-up tilt in patients with tilt-induced neurally mediated syncope (Tilt +ve; n = 31) and in those who tolerated 45 minutes of tilt (Tilt -ve; n = 37).

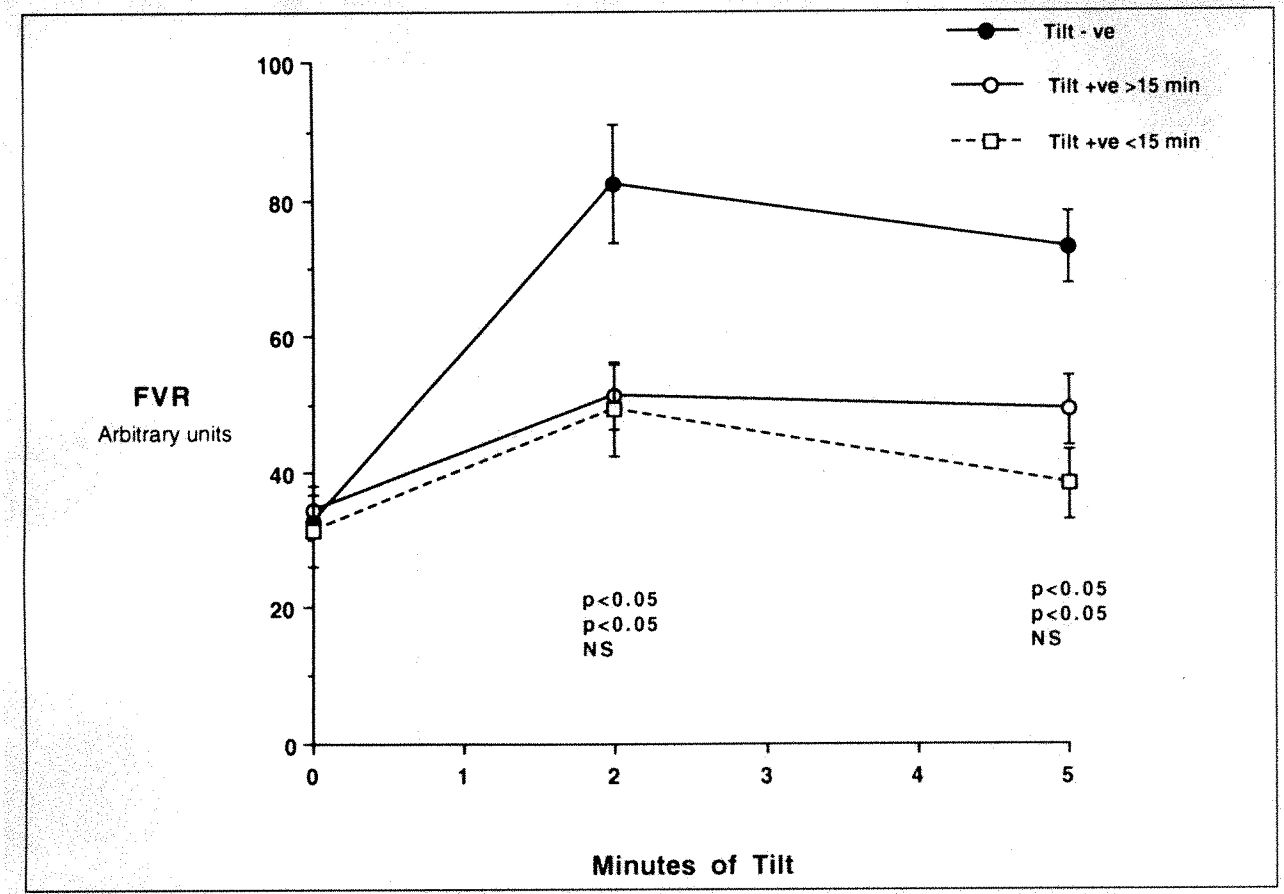


FIGURE 3. Forearm vascular resistance (FVR) at rest and after 2 and 5 minutes of tilt in patients developing syncope between 5 and 15 minutes (Tilt +ve <15 min; n = 15) and after 15 minutes (Tilt +ve >15 min; n = 16), and in those who tolerated 45 minutes of tilt (Tilt -ve; n = 37).

arm blood flow in these cases. The currently accepted mechanism of vasovagal reactions caused by tilt or hemorrhage is that reduced filling pressure and increased inotropic activity leads to firing of ventricular mechanoreceptors.[15] Transmission through unmyelinated C fibers to the brain results in withdrawal of sympathetic tone and augmented vagal activity. During the vasovagal reaction, there is a marked reduction in peripheral resistance with a marked increase in muscle blood flow. In contrast, the limited evidence available suggests that splanchnic vasoconstriction occurs.[16] Cardiac output either remains unchanged or decreases slightly. At the time of syncope, central venous pressure may increase, and 1 study has demonstrated increased peripheral venous tone during syncope.[17,18] It is possible that forearm flow is a more specific marker of tilt-induced hemodynamic instability than total peripheral resistance, because the mechanism of syncope is mediated by muscle rather than splanchnic vasodilation.

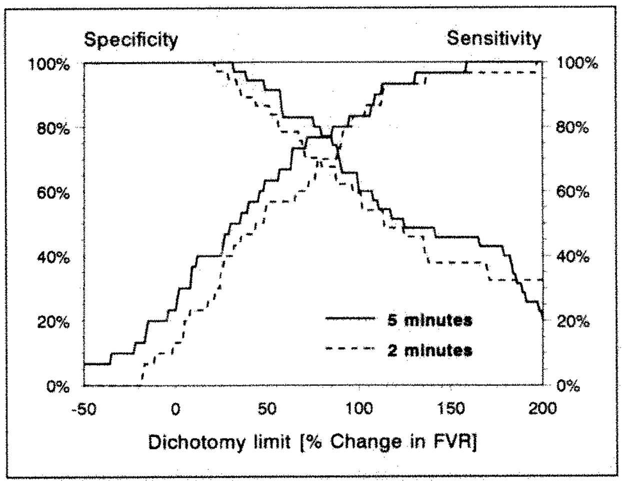


FIGURE 4. Graph of sensitivity and specificity of percent changes in forearm vascular resistance (FVR) at 2 and 5 minutes of tilt in predicting subsequent syncope.

Susceptibility to tilt-induced, neurally mediated syncope: Previously suggested mechanisms of susceptibility to orthostatic stress are reduced blood volume, excessive venous pooling and increased sensitivity to circulating catecholamines.[19–21] If excessive venous pooling alone were the cause, one would expect augmented forearm vasoconstriction immediately after tilt (the reverse of our observations). If augmented catecholamine sensitivity were the cause, augmented heart rate response to tilt would be expected. We observed only a small and insignificant difference in heart rate increase between the 2 groups. Most patients in this study had no evidence of significant cardiac disease, and none had evidence of neuropathy; however, there was a clear difference between the groups well before the onset of the overt vasovagal reaction. It could be argued that the results were biased by the few patients who developed syncope soon after tilting. However, the analysis excluding patients who developed vasovagal reactions within 15 minutes of tilt produced very similar results (Figure 3). It is feasible that our results are due to very early manifestation of a vasovagal reaction, the "phase 1" described by Epstein et al.[17] However, this appears superficially unlikely, because of the time lag to the syncope. The failure of vasoconstriction could be a primary phenomenon responsible for increased susceptibility to tilt-induced vasovagal reactions, possibly due to impaired cardiopulmonary baroreceptor control of muscle blood flow. Decreased systemic vascular resistance would result in smaller ventricular volumes leading to premature triggering of ventricular mechanoreceptors and a positive feedback loop culminating in sudden dramatic vasodilation.[22] However, the abnormality in initial changes in forearm vascular resistance may be merely a marker of increased susceptibility and thus a secondary bystander phenomenon. In patients who are susceptible to tilt-induced vasovagal reactions, it is possible that the cycle of events leading to the final reaction begins very soon after tilting, but only becomes clinically evident much later. This would be consistent with our observation that mean arterial pressure was beginning to decrease at 5 minutes in patients who subsequently had positive tilts compared with those who tolerated the entire 45 minutes. Failure of adequate vasoconstriction and a gradual reduction in blood pressure may explain the presyncopal chronotropic response that has been frequently reported, and the increase in heart rate and possibly contractility providing the final trigger for the vasovagal reaction. It has also been suggested that augmented epinephrine release at the levels observed in response to upright tilt may augment vasodilation[23-25]; this may explain our results, although an excessive chronotropic response in these circumstances would be expected.

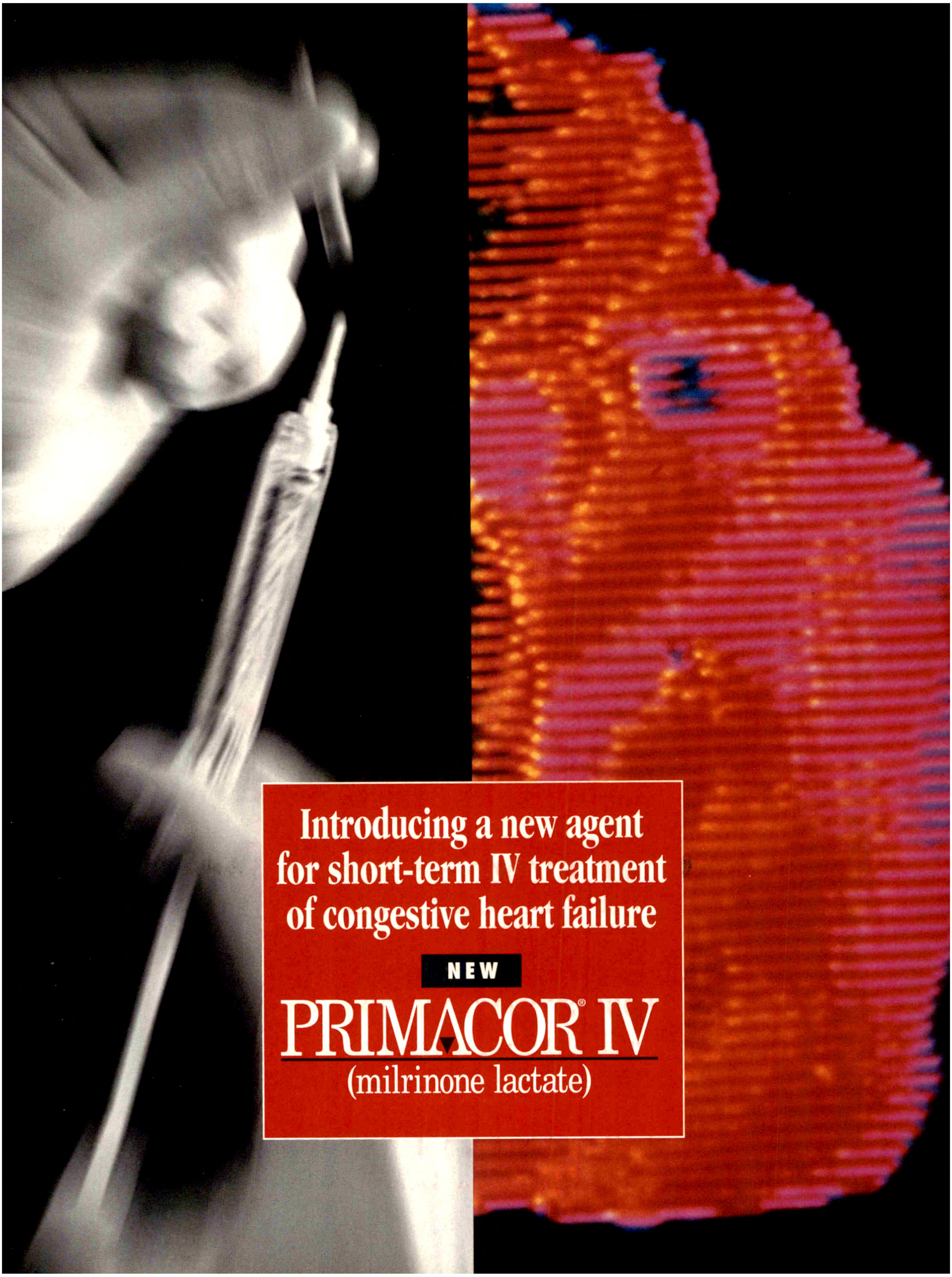
Study implications: The demonstration of abnormal forearm vascular responses immediately after tilt in patients with syncope is a new observation in this patient group. It helps to explain why such patients' syncopal attacks may occur after only brief periods in the upright position. Although further study is needed to explain this abnormality, it is now clear that patients with neurally mediated syncope have impaired circulatory control well before the onset of the classical vasovagal response.

Study limitations: The proportion of patients who developed positive responses to head-up tilt in this study is consistent with that in previous studies, given that isoproterenol was not used and patients were not as rigorously investigated electrophysiologically before tilt testing. This can be explained by the fact that tilt testing is now firmly established as a valuable and simple diagnostic method for the evaluation of syncope and should be performed before invasive studies in patients without evidence of structural heart disease. The duration of tilt was chosen as one that would hopefully be sufficiently sensitive without compromising specificity and without the need for isoproterenol.[26-28] Although this study did not include a group of completely normal control subjects, the purpose was to examine the differences between patients with syncope who also had evidence of postural instability and those who could tolerate orthostatic stress. Both groups consisted largely of patients with structurally normal hearts, and none had evidence of neuropathy.

Acknowledgment: We are indebted to Sheila Gibson, Joan Ward, Anne Staunton and Angela Bygrave for nursing and technical assistance, and to J. Poloniecki, DPhil, for statistical advice.

REFERENCES

1. Anonymous. Explaining syncope. *Lancet* 1991;338:353–354.
2. Almquist A, Goldenberg IF, Milstein S, Chen M-Y, Chen X, Hansen R, Gornick CC, Benditt DG. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med* 1989;320:346–351.
3. Grubb BP, Temesy-Armos P, Hahn H, Elliott L. Utility of upright tilt-table testing in the evaluation and management of syncope of unknown origin. *Am J Med* 1991;90:6–10.
4. Fitzpatrick A, Theodorakis G, Vardas, Kenny RA, Travill CM, Ingram A, Sutton R. The incidence of malignant vasovagal syndrome in patients with recurrent syncope. *Eur Heart J* 1991;12:389–394.
5. Raviele A, Gasparini G, Di Pede F, Delise P, Bonso A, Piccolo E. Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study. *Am J Cardiol* 1990;65:1322–1327.
6. Barcroft H, Edholm OG, McMichael J, Sharpey-Schafer EP. Posthaemorragic fainting. Study by cardiac output and forearm blood flow. *Lancet* 1944;i:489–491.
7. Barcroft H, Edholm OG. On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting. *J Physiol (Lond)* 1945;104:161–175.
8. Schadt JC, Ludbrook J. Hemodynamic and neurohumoral responses to acute hypovolaemia in conscious mammals. *Am J Physiol* 1991;260:H305–H318.
9. Friedman DB, Jensen FB, Matzen S, Secher NH. Non-invasive blood pressure monitoring during head-up tilt using the Penaz principle. *Acta Anaesthesiol Scand* 1990;34:519–522.
10. Whitney RJ. The measurement of volume changes in human limbs. *J Physiol (Lond)* 1953;121:1–27.
11. Greenfield ADM, Whitney RJ, Mowbray JF. Methods for the investigation of peripheral blood flow. *Br Med Bull* 1963;19:101–109.
12. Counihan PJ, Frenneaux MP, Webb DJ, Mckenna WJ. Abnormal vascular responses during supine exercise in hypertrophic cardiomyopathy. *Circulation* 1991;84:656–663.
13. Hainsworth R, Al Shamma YMH. Cardiovascular responses to upright tilting in healthy subjects. *Clin Sci* 1988;74:17–22.
14. Abboud FM, Eckberg DL, Johannsen UJ, Mark AL. Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resitance during venous pooling in man. *J Physiol (Lond)* 1979;286:173–184.
15. van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci* 1991;81:575–586.
16. Grayson J, Swan HJC. Intestinal blood-flow changes in man during fainting. *J Physiol (Lond)* 1951;112:44.
17. Epstein SE, Stampfer M, Beiser GD. Role of capacitance and resistance vessels in vasovagal syncope. *Circulation* 1968;37:524–533.
18. Murray RH, Thompson LJ, Bowers JA, Albright CD. Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. *Am Heart J* 1968;76:799–811.
19. Abi-Samra F, Maloney JD, Fouad-Tarazi FM, Castle LW. The usefulness of head-up tilt testing and hemodynamic investigations in the workup of syncope of unknown origin. *PACE* 1988;11:1202–1214.
20. Hargreaves AD, Muir AL. Lack of variation in venous tone in patients with malignant vasovagal syndrome. *Br Heart J* 1991;66:91.
21. Perry JC, Garson A Jr. The child with recurrent syncope: autonomic testing and beta-adrenergic sensitivity. *J Am Coll Cardiol* 1991;17:1168–1171.
22. Shalev Y, Gal R, Tchou PJ, Anderson AJ, Avitall B, Akhtar M, Jazayeri MR. Echocardiographic demonstration of decreased left ventricular dimensions and vigorous myocardial contraction during syncope induced by head-up tilt. *J Am Coll Cardiol* 1991;18:746–751.
23. Rowell LB, Blackmon JR. Hypotension induced by central hypovolaemia and hypoxaemia. *Clin Physiol* 1989;9:269–277.
24. Sander-Jensen K, Secher NH, Astrup A, Christensen NJ, Giese J, Schwartz TW, Warberg J, Bie P. Hypotension induced by passive head-up tilt: endocrine and circulatory mechanisms. *Am J Physiol* 1986;251:R742–R748.
25. Asso A, Bailin S, Milstein S, Dunnigan A, Remole S, Neustel M, Benditt DG. Epinephrine surge precedes hemodynamic changes in neurally mediated syncope: a possible trigger event (abstr). *Circulation* 1991;84:II-233.
26. Fitzpatrick AP, Theorgorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. *J Am Coll Cardiol* 1991;17:125–130.
27. Nwosu EA, Rahko PS, Hanson P, Grogan EW Jr. The head-up tilt test on isoproterenol is associated with left ventricular cavity obliteration and is frequently positive in healthy adults. *J Am Coll Cardiol* 1992;19:339A.
28. Kapoor WN, Brant N. Evaluation of syncope by upright tilt testing with isoproterenol. A nonspecific test. *Ann Intern Med* 1992;116:358–363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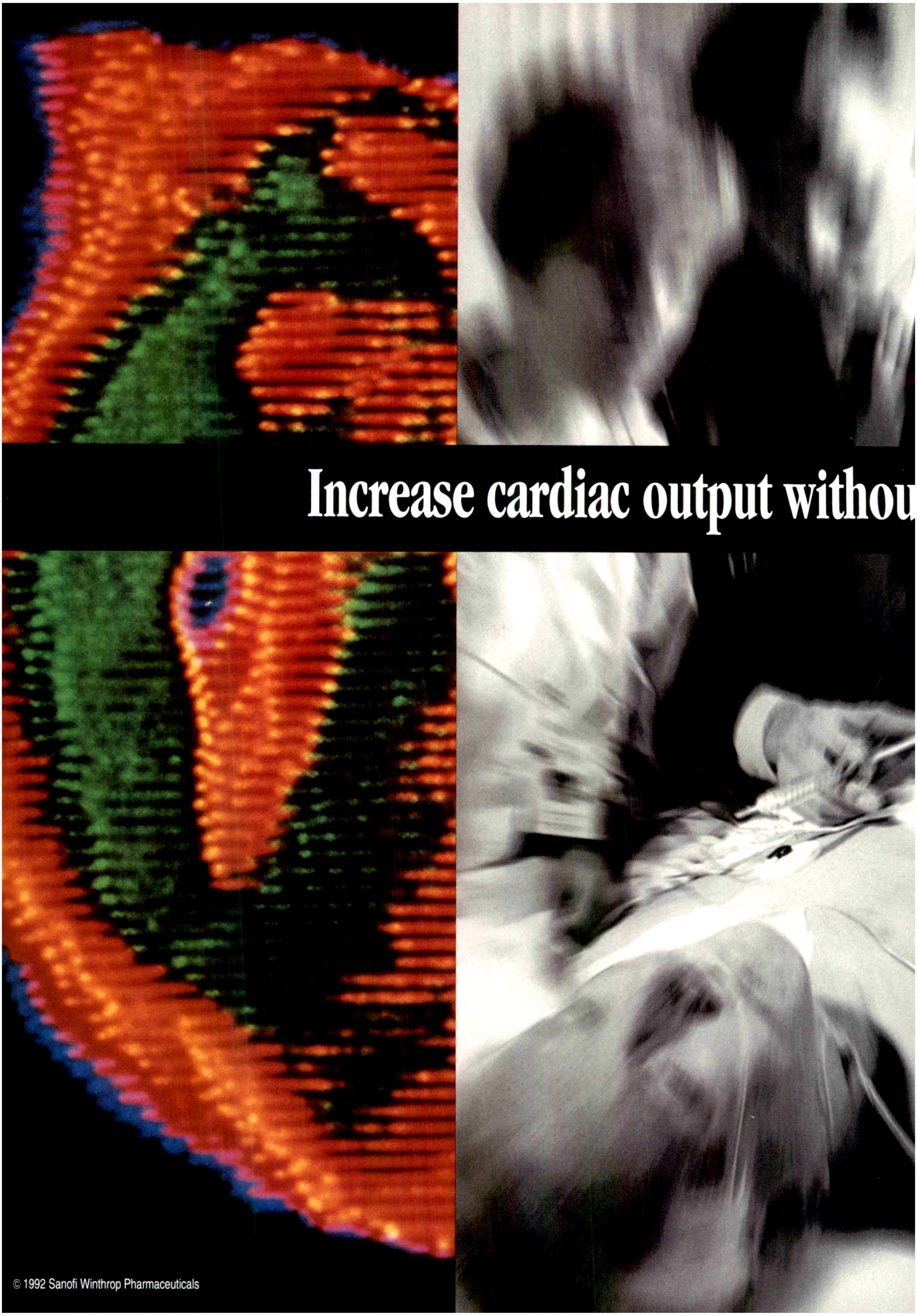

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*Blood pressure and heart rate should be monitored, and the rate of PRIMACOR IV infusion slowed or stopped in patients showing excessive decreases in blood pressure.

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BRIEF SUMMARY

INDICATIONS AND USAGE: PRIMACOR is indicated for the short-term intravenous therapy of congestive heart failure. The majority of experience with intravenous PRIMACOR has been in patients receiving digoxin and diuretics.

In some patients injections of PRIMACOR and oral PRIMACOR have been shown to increase ventricular ectopy, including nonsustained ventricular tachycardia. Patients receiving PRIMACOR should be closely monitored during infusion.

CONTRAINDICATIONS: PRIMACOR is contraindicated in patients who are hypersensitive to it.

PRECAUTIONS: General. PRIMACOR should not be used in patients with severe obstructive aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

Supraventricular and ventricular arrhythmias have been observed in the high-risk population treated. In some patients, injections of PRIMACOR and oral PRIMACOR have been shown to increase ventricular ectopy, including nonsustained ventricular tachycardia. The potential for arrhythmia, present in congestive heart failure itself, may be increased by many drugs or combinations of drugs. Patients receiving PRIMACOR should be closely monitored during infusion.

PRIMACOR produces a slight shortening of AV node conduction time, indicating a potential for an increased ventricular response rate in patients with atrial flutter/fibrillation which is not controlled with digitalis therapy.

During therapy with PRIMACOR, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

If prior vigorous diuretic therapy is suspected to have caused significant decreases in cardiac filling pressure, PRIMACOR should be cautiously administered with monitoring of blood pressure, heart rate, and clinical symptomatology.

USE IN ACUTE MYOCARDIAL INFARCTION. No clinical studies have been conducted in patients in the acute phase of post myocardial infarction. Until further clinical experience with this class of drugs is gained, PRIMACOR is not recommended in these patients.

Laboratory Tests. Fluid and Electrolytes: Fluid and electrolyte changes and renal function should be carefully monitored during therapy with PRIMACOR. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during use of PRIMACOR. **Drug Interactions.** No untoward clinical manifestations have been observed in limited experience where patients in whom PRIMACOR was used concurrently with the following drugs: digitalis glycosides; lidocaine, quinidine; hydralazine, prazosin; isosorbide dinitrate, nitroglycerin; chlorthalidone, furosemide, hydrochlorothiazide, spironolactone; captopril; heparin, warfarin, diazepam, insulin; and potassium supplements. **Chemical Interactions.** There is an immediate chemical interaction which is evidenced by the formation of a precipitate when furosemide is injected into an intravenous line of infusion of PRIMACOR. Therefore, furosemide should not be administered in intravenous lines containing PRIMACOR. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** Twenty-four months of oral administration of PRIMACOR to mice at doses up to 40 mg/kg/day (about 50 times the human oral therapeutic dose in a 50 kg patient) was unassociated with evidence of carcinogenic potential. Neither was there evidence of carcinogenic potential when PRIMACOR was orally administered to rats at doses up to 5 mg/kg/day (about 6 times the human oral therapeutic dose) for twenty-four months or at 25 mg/kg/day (about 30 times the human oral therapeutic dose) for up to 18 months in males and 20 months in females. Whereas the Chinese Hamster Ovary Chromosome Aberration Assay was positive in the presence of a metabolic activation system, results from the Ames Test, the Mouse Lymphoma Assay, the Micronucleus Test, and the in vivo Rat Bone Marrow Metaphase Analysis indicated an absence of mutagenic potential. In reproductive performance studies in rats, PRIMACOR had no effect on male or female fertility at oral doses up to 32 mg/kg/day. **Animal Toxicity.** Oral and intravenous administration of toxic dosages of PRIMACOR to rats and dogs resulted in myocardial degeneration/fibrosis and endocardial hemorrhage, principally affecting the left ventricular papillary muscles. Coronary vascular lesions characterized by periarterial edema and inflammation have been observed in dogs only. The myocardial/endocardial changes are similar to those produced by beta-adrenergic receptor agonists such as isoproterenol, while the vascular changes are similar to those produced by minoxidil and hydralazine. Doses within the recommended clinical dose range (up to 1.13 mg/kg/day) for congestive heart failure patients have not produced significant adverse effects in animals. **Pregnancy Category C.** Oral administration of PRIMACOR to pregnant rats and rabbits during organogenesis produced no evidence of teratogenicity at dose levels up to 40 mg/kg/day and 12 mg/kg/day, respectively. PRIMACOR did not appear to be teratogenic when administered intravenously to pregnant rats at doses up to 3 mg/kg/day (about 2.5 times the maximum recommended clinical intravenous dose) or pregnant rabbits at doses up to 12 mg/kg/day, although an increased resorption rate was apparent at both 8 mg/kg/day and 12 mg/kg/day (intravenous) in the latter species. There are no adequate and well-controlled studies in pregnant women. PRIMACOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers.** Caution should be exercised when PRIMACOR is administered to nursing women, since it is not known whether it is excreted in human milk. **Pediatric Use.** Safety and effectiveness in children have not been established. **Use in Elderly Patients.** There are no special dosage recommendations for the elderly patient. Ninety percent of all patients administered PRIMACOR in clinical studies were within the age range of 45 to 70 years, with a mean age of 61 years. Patients in all age groups demonstrated clinically and statistically significant responses. No age-related effects on the incidence of adverse reactions have been observed. Controlled pharmacokinetic studies have not disclosed any age-related effects on the distribution and elimination of PRIMACOR.

ADVERSE REACTIONS: Cardiovascular Effects: In patients receiving PRIMACOR in Phase II and III clinical trials, ventricular arrhythmias were reported in 12.1%: Ventricular ectopic activity, 8.5%; nonsustained ventricular tachycardia, 2.8%; sustained ventricular tachycardia, 1% and, ventricular fibrillation, 0.2% (2 patients experienced more than one type of arrhythmia). Holter recordings demonstrated that in some patients injection of PRIMACOR increased ventricular ectopy, including nonsustained ventricular tachycardia. Life-threatening arrhythmias were infrequent and when present have been associated with certain underlying factors such as preexisting arrhythmias, metabolic abnormalities (e.g. hypokalemia), abnormal digoxin levels and catheter insertion. PRIMACOR was not shown to be arrhythmogenic in an electrophysiology study. Supraventricular arrhythmias were reported in 3.8% of the patients receiving PRIMACOR. The incidence of both supraventricular and ventricular arrhythmias has not been related to the dose or plasma milrinone concentration. Other cardiovascular adverse reactions include hypotension, 2.9% and angina/chest pain, 1.2%. **CNS Effects.** Headaches, usually mild to moderate in severity, have been reported in 2.9% of patients receiving PRIMACOR. **Other Effects.** Other adverse reactions reported, but not definitely related to the administration of PRIMACOR include hypokalemia, 0.6%; tremor, 0.4%; and thrombocytopenia, 0.4%.

OVERDOSAGE: Doses of PRIMACOR may produce hypotension because of its vasodilator effect. If this occurs, administration of PRIMACOR should be reduced or temporarily discontinued until the patient's condition stabilizes. No specific antidote is known, but general measures for circulatory support should be taken.

DOSAGE AND ADMINISTRATION: PRIMACOR should be administered with a loading dose followed by a continuous infusion (maintenance dose) according to the following guidelines:

LOADING DOSE
50 μg/kg: Administer slowly over 10 minutes

MAINTENANCE DOSE

	Infusion Rate	Total Daily Dose (24 Hours)	
Minimum	0.375 μg/kg/min	0.59 mg/kg	Administer as a continuous intravenous infusion.
Standard	0.50 μg/kg/min	0.77 mg/kg	
Maximum	0.75 μg/kg/min	1.13 mg/kg	

The infusion rate should be adjusted according to hemodynamic and clinical response. Patients should be closely monitored. In controlled clinical studies, most patients showed an improvement in hemodynamic status as evidenced by increases in cardiac output and reductions in pulmonary capillary wedge pressure.

Note: See "**Dosage Adjustment in Renally Impaired Patients.**" Dosage may be titrated to the maximum hemodynamic effect and should not exceed 1.13 mg/kg/day. Duration of therapy should depend upon patient responsiveness.

Intravenous infusions of PRIMACOR should be administered as described in the following chart.

PRIMACOR–RATES OF INFUSION
FOR CONCENTRATIONS OF 100 μg/mL, 150 μg/mL, AND 200 μg/mL
INFUSION DELIVERY RATE

PRIMACOR (μg/kg/min)	100 μg/mL* (mL/kg/hr)	150 μg/mL** (mL/kg/hr)	200 μg/mL† (mL/kg/hr)
0.375	0.22	0.15	0.11
0.400	0.24	0.16	0.12
0.500	0.30	0.20	0.15
0.600	0.36	0.24	0.18
0.700	0.42	0.28	0.21
0.750	0.45	0.30	0.22

In order to calculate flow rate (milliliters per hour), multiply infusion delivery rate times patient weight (in kilograms).

*Prepare by adding 180 mL diluent per 20 mg vial (20 mL) PRIMACOR.

**Prepare by adding 113 mL diluent per 20 mg vial (20 mL) PRIMACOR.

†Prepare by adding 80 mL diluent per 20 mg vial (20 mL) PRIMACOR.

Note: Diluents which may be used to prepare dilutions of PRIMACOR for intravenous infusion are 0.45% Sodium Chloride Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose Injection USP.

Intravenous drug products should be inspected visually and should not be used if particulate matter or discoloration is present.

Dosage Adjustment in Renally Impaired Patients. Data obtained from patients with severe renal impairment (creatinine clearance = 0 to 30 mL/min) but without congestive heart failure have demonstrated that the presence of renal impairment significantly increases the terminal elimination half-life of PRIMACOR. Reductions in infusion rate may be necessary in patients with renal impairment. For patients with clinical evidence of renal impairment, the recommended infusion rate can be obtained from the following Table:

Creatinine Clearance (mL/min/1.73 m²)	Infusion Rate (μg/kg/min)
5	0.20
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

Revised July 1992

PSW-1 E

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REFERENCES: 1. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation.* 1986;73(suppl III):168–174. **2.** Biddle TL, Benotti JR, Creager MA, et al. Comparison of intravenous milrinone and dobutamine for congestive heart failure secondary to either ischemic or dilated cardiomyopathy. *Am J Cardiol.* 1987;59:1345–1350. **3.** Anderson JL. Hemodynamic and clinical benefits with intravenous milrinone in severe chronic heart failure: results of a multicenter study in the United States. *Am Heart J.* 1991;121:1956–1964. **4.** PRIMACOR IV Prescribing Information. Sanofi Winthrop Pharmaceuticals. **5.** Jaski BE, Fifer MA, Wright RF, Braunwald E, Colucci WS. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure: dose-response relationships and comparison to nitroprusside. *J Clin Invest.* 1985;75:643–649. **6.** Baim DS, McDowell AV, Cherniles J, et al. Evaluation of a new bipyridine inotropic agent — milrinone — in patients with severe congestive heart failure. *N Engl J Med.* 1983;309:748–756. **7.** Colucci WS, Denniss AR, Leatherman GF, et al. Intracoronary infusion of dobutamine to patients with and without severe congestive heart failure: dose-response relationships, correlation with circulating catecholamines, and effect of phosphodiesterase inhibition. *J Clin Invest.* 1988;81:1103–1110. **8.** Ludmer PL, Wright RF, Arnold JMO, Ganz P, Braunwald E, Colucci WS. Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique. *Circulation.* 1986;73:130–137. **9.** Sonnenblick EH, Grose R, Strain J, Zelcer AA, LeJemtel TH. Effects of milrinone on left ventricular performance and myocardial contractility in patients with severe heart failure. *Circulation.* 1986;73(suppl III):162–167. **10.** Grose R, Strain J, Greenberg M, LeJemtel TH. Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. *J Am Coll Cardiol.* 1986;7:1107–1113. **11.** Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossman W. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation.* 1985;71:972–979.

60-226860B

A Population-Based Estimate of Candidacy Rates for the Implantable Cardioverter-Defibrillator

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The implantable cardioverter-defibrillator (ICD) increases survival of patients who receive the device. However, candidacy rates have not been calculated for a defined population, and the potential effect of the device on the survival of all patients with heart disease has not been estimated. To make these calculations, medical records were reviewed for 1976 to 1988 in a population demographically similar to the white population of the United States. Definite and possible candidates were identified on the basis of American Heart Association/American College of Cardiology guidelines. Candidacy rates ranged from 3.3/100,000 (counting only definite candidates for the entire period) to 8.7/100,000 (counting definite and possible candidates after 1980). Extrapolated to the 1990 U.S. population, estimates ranged from 8,207 to 21,637 new candidates each year. During an average follow-up of 5 years, half of all deaths among candidates had the potential to be delayed by an ICD. In a similar population that has a death rate from heart disease of approximately 280/100,000, 0.6 to 1.6% of subjects have the potential to have their deaths delayed to some extent by an ICD.

(Am J Cardiol 1993;71:77–81)

An automatic defibrillator was first implanted in a human in 1980[1] in an attempt to prevent recurrent sudden death, and several case series[2–9] suggest that the implantable cardioverter-defibrillator (ICD) can reduce mortality rates in the first year after primary ventricular fibrillation from >30 to ≤10%. Operative mortality for implantation is approximately 2 to 3%,[2–4] and long-term complication rates are reported to be similar to those for pacemaker patients.[5] The cost-effectiveness ratio of this device is within the range of currently accepted medical therapies.[10–12] Although 9,000 devices were implanted in subjects in the United States in 1991 (unpublished data; data bases of Cardiac Pacemakers, Inc., Telectronics and Medtronics), it has been suggested that the potential pool of candidates is much larger.[13] This report estimates the size of the pool from a defined population that is demographically similar to the white population of the U.S. and extrapolates these rates to the U.S. population. It also describes the survival of ICD candidates and estimates the potential of the ICD to delay deaths in patients with heart disease.

METHODS

The population used for this study was approximately 60,000 people residing in a city in the midwestern U.S. Indexes are maintained for all diagnoses and procedures recorded by the medical care providers serving these residents.[14] The inpatient and outpatient medical records of each patient can be retrieved, enabling review of all clinical notes recorded by health care providers in the community. All residents with conditions such as clinically recognized ventricular tachycardia and ventricular fibrillation can be identified with this system.

To identify potential candidates for an ICD, the following sources were searched for the 13 years from January 1, 1976, through December 31, 1988: diagnostic indexes, the amiodarone study register, the cardiac electrophysiology study register and the ambulance service reports of the 1 company that supplies all advanced life support services for the city. These lists were searched for subjects who fulfilled the American College of Cardiology/American Heart Association (ACC/AHA) criteria for implantation of an automatic ICD.[15] Patients were considered potential candidates if they: (1) had been resuscitated from a cardiac arrest, (2) had hemodynamically unstable, sustained ventricular tachycardia, or (3) had syncope associated with nonsustained ventricular tachycardia.

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TABLE I Distribution of Qualifying and Disqualifying Conditions* Among 142 Potential Candidates Identified by the Initial Review of Records

	Qualifying Conditions		
	Cardiac Arrest Survivor	Sustained VT	Syncope and Nonsustained VT
Total events	122	16	4
Reason for disqualification			
Died without leaving hospital	72	0	2
Nonfatal myocardial infarction	19	0	0
Too debilitated for testing or ICD insertion	2	3	1
Reversible cause for VT or ventricular fibrillation	1	0	0
Candidates with no disqualifying condition	28	13	1

*Qualifying conditions were assigned following hierarchy in descending order: cardiac arrest survivor, sustained VT, and syncope associated with nonsustained VT. Disqualifying conditions were assigned following hierarchy in descending order: died in hospital, myocardial infarction precipitated event, too debilitated for electrophysiologic testing or insertion of ICD, and reversible cause of event.

ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.

Patients were not considered candidates if: (1) cardiac arrest was associated with acute myocardial infarction (defined as the development of new Q waves or a creatine kinase MB isoenzyme level >4% of the total creatine kinase level, or both), drug overdose or intoxication, antiarrhythmic medications, electrolyte abnormalities or hypoxemia; (2) they were too debilitated to undergo electrophysiologic testing or ICD implantation; or (3) they had not lived in the city for a full year before the qualifying event. This last criterion was included in all studies in this population to exclude patients who moved into the community for treatment of their medical problems. This population-based analysis evaluated only residents of the city and excluded all patients referred for treatment from outside the community.

Most candidates qualified for multiple reasons (e.g., cardiac arrest and hemodynamically unstable, sustained ventricular tachycardia). Therefore, to list 1 cause for a patient's candidacy, the inclusion criteria were ranked in the following descending hierarchy: cardiac arrest, hemodynamically significant, sustained ventricular tachycardia, and syncope associated with nonsustained ventricular tachycardia.

Candidates who fulfilled ≥1 inclusion criterion and no exclusion criterion were further classified as definite (AHA/ACC criteria class I) or possible (class II) on the basis of the number of drugs tested and the results of electrophysiologic testing. Candidates with history of cardiac arrest in whom neither ventricular fibrillation nor tachycardia could be induced while receiving no antiarrhythmic drugs were defined as definite candidates. Candidates in whom either ventricular fibrillation or tachycardia could be induced during ≥2 studies with drugs other than intravenous procainamide were also defined as definite candidates. Candidates who had no exclusion criteria, but did not fulfill the electrophysiologic testing criteria for definite candidacy (e.g., because they did not have a baseline electrophysiologic test and testing of 2 drugs other than intravenous procainamide) were defined as possible candidates.

Because electrophysiologic testing was more routinely used in this population after 1980 and because electrophysiologic testing was required for a subject to be a definite candidate, the candidacy rates were calculated for both the total period from 1976 through 1988 and the period after 1980. Simple linear regression was used to test whether there was a trend for the number of candidates to increase by calendar year.

Decennial census data[16,17] were used to calculate age- and sex-specific candidacy rates for definite and possible candidates, and for both groups combined. Ninety-five percent confidence intervals (CI) for these rates were estimated from the cumulative Poisson distribution.[18]

Actuarial survival was calculated by the Kaplan-Meier method for definite and possible candidates, and for potential ones who were excluded because their cardiac arrest was associated with an acute myocardial infarction. To determine whether definite and possible ICD candidates were truly at high risk of death, the 3 survival curves were compared using the log-rank test.

The potential of the ICD to influence mortality in the population of ICD candidates was then estimated. It was assumed that subjects who had received an "appropriate" shock from an ICD had had their lives extended by their ICD. It was also assumed that subjects who died suddenly out of the hospital without an ICD may have had their lives extended by an ICD. The sum of these 2 groups was divided by the total number of subjects who had died plus the number of those who were alive and had received an appropriate shock from their ICD. This proportion was multiplied by the ICD candidacy rates to estimate the rate for the entire population at which the ICD may prolong lives. This calculation maximizes the estimated potential benefit from the ICD. Because of the small number of patients who actually received the ICD, no attempt was made to characterize its impact on the life expectancy of a candidate.

To provide perspective to the candidacy rates and the estimated impact of the ICD on death rates from heart disease, these death rates were calculated for the city for 1978 and were directly adjusted to the 1980 U.S. population. The adjusted rates were compared with the rates of ICD candidacy and deaths delayed by the ICD. To estimate the number of subjects in the U.S. who may fulfill the ACC/AHA criteria for ICDs each year, the age- and sex-specific rates for the city were directly age- and sex-adjusted to the population structure of United States whites in 1990 and multiplied by the total U.S. population.

RESULTS

Qualifying and disqualifying conditions: Review of the records identified 142 subjects (age range 31 to 93 years, mean 67.4 ± 12.0) with ≥1 qualifying condition for an ICD. Women constituted 27% of the group. One hundred twenty-two subjects had been resuscitated from cardiac arrest, 16 had hemodynamically unstable, sustained ventricular tachycardia, and 4 had syncope associated with nonsustained ventricular tachycardia (Table I).

One hundred of the 142 patients were disqualified, including 74 who died in the hospital, 19 who had a cardiac arrest in association with an acute myocardial infarction and left the hospital alive, 1 who developed ventricular fibrillation as a result of choking on an apple, and 6 who were too debilitated for electrophysiologic testing and the ICD implantation procedure. The remaining 42 patients (mean age 65.1 ± 10.7 years, range 36 to 81) were either definite or possible candidates. Women constituted 22% of the candidates.

Rates of definite and possible candidacy: Nineteen patients fulfilled the criteria for definite and 23 for possible candidacy. Approximately half (10 of 19) of the definite candidates had had an out-of-hospital cardiac arrest; the remaining 9 presented with hemodynamically unstable, sustained ventricular tachycardia. Eighteen of the 23 possible candidates presented with out-of-hospital cardiac arrest, 4 with sustained ventricular tachycardia, and 1 with syncope associated with nonsustained ventricular tachycardia.

Over the period from 1976 to 1988, the rates of definite and possible candidacy were 3.3 and 4.0/100,000 person-years, respectively (Table II). The combined rate of definite and possible candidacy based on the 1976 to 1988 period was 7.3/100,000 person-years. After 1980, the candidacy rates were 4.8 and 3.9/100,000 person-years for definite and possible candidates, respectively, and 8.7/100,000 person-years for the 2 groups combined. There was a trend for the number of definite candidates to increase in later years ($p < 0.002$), but there was no trend for the number of possible candidates to increase over time ($p = 0.86$).

TABLE II Incidence Rates (per 100,000 person-years, age- and sex-adjusted to 1980 U.S. population) of Definite and Possible Candidacy Based on Entire Period (1976 to 1988) and 1981 to 1988 Period

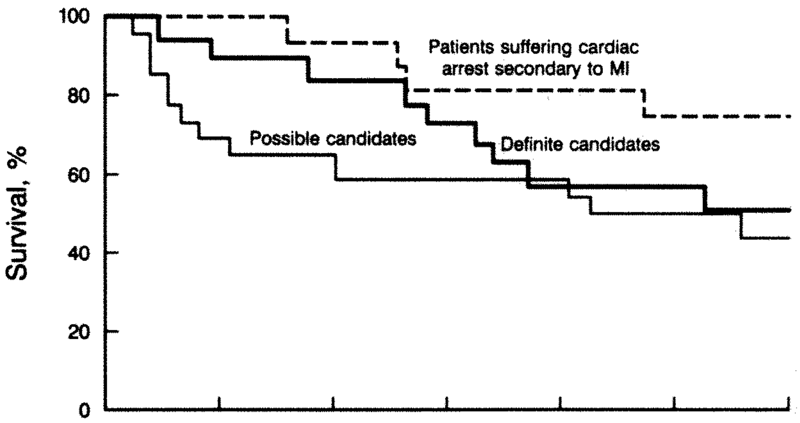
	Candidacy		
Period	Definite	Possible	Total
1976 to 1988			
Point estimate	3.3	4.0	7.3
95% CI	1.8 to 4.8	2.3 to 5.6	5.0 to 9.5
1981 to 1988			
Point estimate	4.8	3.9	8.7
95% CI	2.6 to 7.1	1.9 to 5.9	5.7 to 11.7

CI = confidence interval.

Mortality: Mortality was not different for definite and possible ICD candidates ($p = 0.57$), but mortality rates were significantly higher for ICD candidates than for subjects who had had cardiac arrest in association with myocardial infarction ($p < 0.05$; Figure 1). One-year survival for definite candidates was 89%, and 5-year survival was 58%. Survival for possible candidates was 70 and 51% at 1 and 5 years, respectively. All patients who were discharged alive after a cardiac arrest due to acute myocardial infarction were alive after 1 year, and 5-year survival for these patients was 75% (Figure 1).

Eight of 19 definite and 8 of 23 possible candidates were alive at the last follow-up (Table III). Four definite and 6 possible candidates had died suddenly out of the hospital without an ICD.

Both definite candidates who were still alive with ICDs, 1 definite candidate who died in the hospital with an ICD, and 1 possible candidate who died suddenly out of the hospital with an ICD had received appropriate shocks while alive. The 1 definite candidate who died out of the hospital with an ICD, and 1 of 2 who died in the hospital never received appropriate shocks.



Years	0	1	2	3	4	5	6
Definite candidates	19	16	14	11	9	8	6
Possible candidates	23	16	14	13	13	11	8
Patients suffering cardiac arrest secondary to MI	19	18	16	14	13	11	10

FIGURE 1. Six-year life-table survival for patients who left hospital alive after cardiac arrest due to acute myocardial infarction (MI) for definite and possible implantable cardioverter-defibrillator (ICD) candidates. Mortality was not significantly different for definite and possible ICD candidates (p = 0.57). Mortality rates were significantly higher for ICD candidates than for patients who had cardiac arrest in association with myocardial infarction (p <0.05).

TABLE III Survival and Causes of Mortality for Definite and Possible Implantable Cardioverter-Defibrillator (ICD) Candidates

	Definite	Possible
Alive	8	8
With ICD	2	—
Dead	11	15
Acute myocardial infarction	—	1
Congestive heart failure	3	6
Sudden out-of-hospital without ICD	4	6
Sudden out-of-hospital with ICD	1	1
In-hospital with ICD	2	—
Noncardiac (cancer)	1	1

Extrapolation from observed events: We assumed that the 4 subjects with appropriate shocks from their ICDs had their lives prolonged and that all 10 who died suddenly out of the hospital may have had their lives extended by an ICD. Based on these assumptions, we calculated that 50% (the aforementioned 14 patients in the numerator, and 26 deaths plus the 2 patients alive with ICDs after appropriate shocks in the denominator) of the deaths in this group may have been delayed by implanting an ICD (95% CI 32 to 68%). Multiplying this figure of 50% by the candidacy rates produced an estimate that 1.7 to 4.4/100,000 persons in a population may have their deaths delayed to some extent by an ICD.

The mortality rate from heart disease during this period in the city (adjusted to the 1980 U.S. population) was 280/100,000 persons for the entire population (unpublished analysis). Therefore, the estimated impact of the ICD on cardiac mortality ranges from 0.6 to 1.6% for the entire population.

Extrapolation of the candidacy rates to the entire population of the U.S. produced a minimal estimate (based only on definite candidates during the entire period of observation) of 8,207 new candidates per year (95% CI 4,477 to 11,937). The highest estimate (based on definite plus possible candidates from only the years 1981 to 1988) was 21,637 new candidates per year (95% CI 14,176 to 29,098).

DISCUSSION

The experience in this population between 1976 and 1988 suggests that the candidacy rate for the ICD in the U.S. population is between 3.3 and 8.7 devices/100,000 persons each year. This translates into an estimate of ≤21,637 new ICD candidates in the U.S. each year. If all candidates receive an ICD, and half of them have their lives extended by the device, ≤1.6% of the population dying of heart disease would have their lives extended to some extent by an ICD. It is beyond the scope of the current data set to define how great that extent may be.

There are reasons to believe that the higher, rather than the lower, estimated candidacy rates will be closest to the future ICD use rates. First, the sudden death rate among possible candidates is at least as high as that among definite ones. Second, death rates for heart disease for the region of this population are less than those for the country as a whole,[19] and the rates of cardiac arrest survival in this study are less than those reported in other studies.[20] Third, death rates in the post–cardiac arrest population are high even when ventricular tachycardia can be suppressed by drugs during electrophysiologic testing,[21] and many patients develop toxicity with long-term amiodarone treatment. Finally, transvenous lead systems and advanced antiarrhythmia devices have been very successful.[22] If current trials in patients with the triad of ischemic heart disease, left ventricular dysfunction and inducible ventricular tachycardia show that treatment with an ICD reduces mortality, the pool of ICD candidates will be enlarged even further.

Although the ICD may markedly change the life expectancy of candidates, the data suggest that a relatively low percentage of patients with heart disease have the potential to benefit from the device. Doubling the calculated rates would not increase the potential impact on mortality by much more than 3% of all deaths from cardiac disease in the population. The impact on total mortality would be less than half this size. Thus, this analysis suggests that the ICD is an example of a therapy that has significant potential to delay the death of a candidate, but it has only a small potential for having an effect on the life of the average subject who develops heart disease.

REFERENCES

1. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322–324.

2. Winkle RA, Mead RH, Ruder MA, Gaudiani VA, Smith NA, Buch WS, Schmidt P, Shipman T. Long-term outcome with the automatic implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1989;13:1353–1361.

3. Fogoros RN, Fiedler SB, Elson JJ. The automatic implantable cardioverter- defibrillator in drug-refractory ventricular tachyarrhythmias. *Ann Intern Med* 1987;107:635–641.

4. Manolis AS, Tan-DeGuzman W, Lee MA, Rastegar H, Haffajee CI, Huang SKS, Estes NAM III. Clinical experience in 77 patients with the automatic implantable cardioverter defibrillator. *Am Heart J* 1989;118:445–450.

5. Thomas AC, Moser SA, Smutka ML, Wilson PA. Implantable defibrillation: eight years of clinical experience. *PACE* 1988;11:2053–2058.

6. Tchou PJ, Kadri N, Anderson J, Caceres JA, Jazayeri M, Akhtar M. Automatic implantable cardioverter defibrillators and survival of patients with left ventricular dysfunction and malignant ventricular arrhythmias. *Ann Intern Med* 1988;109:529–534.

7. Borbola J, Denes P, Ezri MD, Hauser RG, Serry C, Goldin MD. The automatic implantable cardioverter-defibrillator. Clinical experience, complications, and follow-up in 25 patients. *Arch Intern Med* 1988;142:70–76.

8. Kim SG, Fisher JD, Furman S, Gross J, Zilo P, Roth JA, Ferrick KJ, Brodman R. Benefits of implantable defibrillators are overestimated by sudden death rates and better represented by the total arrhythmic death rate. *J Am Coll Cardiol* 1991;17:1587–1592.

9. Schaffer WA, Cobb LA. Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. *N Engl J Med* 1975;293:259–262.

10. Kuppermann M, Luce BR, McGovern B, Podrid PJ, Bigger JT Jr, Ruskin JN. An analysis of the cost effectiveness of the implantable defibrillator. *Circulation* 1990;81:91–100.

11. Larsen GC, Manolis AS, Sonnenberg FA, Beshansky JR, Estes NAM, Pauker SG. Cost-effectiveness of the implantable cardioverter-defibrillator: effect of improved battery life and comparison with amiodarone therapy. *J Am Coll Cardiol* 1992;19:1323–1334.

12. O'Donoghue S, Platia EV, Brooks-Robinson S, Mispireta L. Automatic implantable cardioverter-defibrillator: is early implantation cost-effective? *J Am Coll Cardiol* 1990;16:1258–1263.

13. Mower MM, Nisam S. AICD indications (patient selection): past, present and future. *PACE* 1988;11:2064–2070.

14. Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am* 1981;245:54–63.

15. Dreifus LS, Fisch C, Griffin JC, Gillette PC, Mason JW, Parsonnet V. Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. (Committee on Pacemaker Implantation). *Circulation* 1991;84:455–467.

16. Schroeder DJ, Offord KP. A SAS Macro which utilizes local and reference population counts appropriate for incidence, prevalence, and mortality rate calculations in Rochester and Olmsted County, Minnesota. Technical Report Series, No. 20, Section of Medical Research Statistics, Mayo Clinic, Rochester, Minnesota, August 1982.

17. Bergstralh EJ, Offord KP. Projected Rochester and Olmsted County populations for 1981–1985. Technical Report Series, No. 38, Section of Medical Research Statistics, Mayo Clinic, Rochester, Minnesota, February 1988.

18. Beyer WH, ed. C.R.C. Handbook of Tables for Probability and Statistics. Cleveland: Chemical Rubber Company, 1966:58–64.

19. Gillum RF, Hannan PJ, Prineas RJ, Jacobs DR, Gomez-Marin O, Luepker RV, Baxter J, Kottke TE, Blackburn H. Coronary heart disease mortality trends in Minnesota: 1960–80: The Minnesota Heart Survey. *Am J Public Health* 1984;74:360–362.

20. Cobb LA. Survival after cardiac arrest. In: Higgins MW, Luepker RV, eds. Trends in Coronary Heart Disease Mortality. The Influence of Medical Care. New York: Oxford University Press, 1988:152–159.

21. Fogoros RN, Elson JJ, Bonnet CA, Fiedler SB, Chenarides JG. Long-term outcome of survivors of cardiac arrest whose therapy is guided by electrophysiologic testing. *J Am Coll Cardiol* 1992;19:780–788.

22. Bardy GH, Troutman C, Poole JE, Kudenchuk PJ, Dolack GL, Johnson G, Hofer B. Clinical experience with a tiered-therapy, multiprogrammable antiarrhythmia device. *Circulation* 1992;85:1689–1698.

Efficacy and Tolerability of Lovastatin in Hypercholesterolemia in Patients with Systemic Hypertension

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A previously published study reported on an open-label, multicenter study of the efficacy and tolerability of lovastatin in the management of nonfamilial primary hypercholesterolemia. In the present report the results from the 213 hypercholesterolemic patients with systemic hypertension are presented. At baseline mean ± SD of total serum cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and the ratio of total serum cholesterol to HDL cholesterol were 268 ± 24, 189 ± 22 and 43 ± 10 mg/dl and 6.6 ± 1.6, respectively. Of the 213 hypertensive patients only 24 were not receiving antihypertensive or related cardiac medication. Baseline mean systolic and diastolic blood pressures were 140 ± 20 and 84 ± 9 mm Hg, respectively. Within 1 month of lovastatin therapy the observed significant reductions in total serum cholesterol, low-density lipoprotein cholesterol and the ratio of total to HDL cholesterol were 19, 27 and 24%, respectively. HDL cholesterol was increased by 6%. Diastolic blood pressure did not change significantly during this 1-month period. The 1-month lipid results were maintained over the full 6 months of the study. The dosage of lovastatin was 20 mg/day for the first month of therapy and could subsequently be adjusted to response, up to a maximum of 80 mg/day. Again, without changes in diastolic blood pressure, lovastatin was generally effective in improving the serum lipids of hypercholesterolemic hypertensive patients regardless of the type of antihypertensive medications received (including diuretics and β blockers). Lovastatin was generally well tolerated.

(Am J Cardiol 1993;71:82–87)

Systemic hypertension is an established risk factor for coronary artery disease.[1,2] Blood pressure reduction in animal studies retards the progress of coronary artery disease.[3] However, clinical trials of antihypertensive agents have not been consistently beneficial,[4] possibly because of the development of an unfavorable lipid profile.[5–7] In a previous publication we reported the results of a multicenter study of 489 adult patients with hypercholesterolemia.[8] Because there are very few published reports on the efficacy and tolerability of lovastatin in hypercholesterolemic patients with hypertension, we thought it appropriate to assess retrospectively the response of this subset of patients and examine the efficacy of lovastatin in reducing blood lipids in hypercholesterolemic hypertensive patients taking a variety of antihypertensive agents.

METHODS

Design: The study design was a multicenter, open-label, prospective study involving 40 centers and was described in a recent publication.[8] Patients aged ≥21 years not on a cholesterol-reducing diet, with total cholesterol levels ≥240 mg/dl and LDL cholesterol levels ≥190 mg/dl, or ≥160 mg/dl with definite coronary artery disease or 2 other coronary artery disease risk factors, were given a standard (e.g., National Cholesterol Education Program step I or American Heart Association phase I) cholesterol-reducing diet and had all lipid-lowering agents withdrawn.

After 6 weeks of the diet-only (baseline) period, those for whom further attempts to reduce serum cholesterol by diet and other nonpharmacologic measures alone were considered ineffective, were enrolled in the diet plus lovastatin treatment phase. Evaluations of serum lipids, clinical parameters, blood chemistry and adverse effects were made every month during the 6-month diet plus lovastatin treatment period. The dosage of lovastatin was 20 mg/day for the first month and could subsequently be adjusted up to a maximum of 80 mg/day according to the response of the patients and the judgment of the participating physicians. A total of 213 hypercholesterolemic patients with hypertension were studied. These patients were identified as hypertensive by the participating physicians based on their medical history and the physical examination performed during the initial screening. We report in detail on the response of these patients to lovastatin therapy.

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Objective: The objective of this report was to evaluate the efficacy and tolerability of lovastatin in hypercholesterolemic hypertensive patients, especially in those receiving concurrent therapy indicated by the physician for hypertension, and for the various types of antihypertensive medications received (i.e., diuretics, β blockers, angiotensin-converting enzyme inhibitors or other antihypertensive drugs). The lipid variables under consideration are total, LDL and high-density lipoprotein (HDL) cholesterol, the ratio of total cholesterol to HDL cholesterol, and triglycerides. Baseline serum lipid values were lipid values obtained after the diet-only period. The changes from baseline observed after 1 month of lovastatin therapy were of primary interest.

Statistical analysis: The paired *t* test was used to test whether cholesterol levels after 1 month of lovastatin therapy showed significant improvement over baseline values for all hypertensive patients, and within each subgroup of the hypertensive patients. All tests were 2-tailed. The 0.05 level was used for statistical significance.

RESULTS

Baseline in all hypertensive patients: Of the 213 hypercholesterolemic hypertensive patients, 127 were women (60%) and 86 were men (40%). Mean age ± SD was 59 ± 11 years (range 25 to 83). At baseline, mean systolic blood pressure was 140 ± 20 mm Hg and mean diastolic blood pressure 84 ± 9 mm Hg. Forty-eight percent of these patients reported a family history of premature coronary artery disease, 13% smoked cigarettes, 24% had low HDL cholesterol (<35 mg/dl), 13% had diabetes mellitus, 11% had a history of cerebrovascular or occlusive peripheral vascular disease, and 14% were obese (i.e., >30% overweight).

Of the 213 patients, 189 (89%) were receiving drug therapy determined by the study physicians to be given to them because of their hypertension. Most patients were receiving more than 1 type of drug therapy. Table I contains data on the different types of medications received by these patients. These medications included not only the usual antihypertensive drugs (i.e., diuretics, β blockers and angiotensin-converting enzyme inhibitors), but also cardiac and other drugs that were prescribed to counteract the increased risk of coronary artery disease due to hypertension. Of the 189 hypertensive patients receiving antihypertensive or related cardiac drugs, 26 were receiving only cardiac or other medications (e.g., aspirin). The remaining 163 were receiving medications aimed at controlling their high blood pressure including diuretics (102 patients), β blockers (67 patients), angiotensin-converting enzyme inhibitors (39 patients), and other antihypertensive drugs (10 patients).

TABLE I Drug Therapy Among Hypertensive Patients (n = 189)

Drugs	No. (%)
Only diuretic	27 (14)
Only β blocker	17 (9)
Only cardiac	16 (8)
Only ACE inhibitors	9 (5)
Only other antihypertensive	2 (1)
Only other	1 (1)
Diuretic + β blocker	5 (3)
Diuretic + cardiac	10 (5)
Diuretic + ACE inhibitors	8 (4)
Diuretic + other antihypertensive	2 (1)
Diuretic + other	16 (8)
β blocker + other	8 (4)
β blocker + cardiac	8 (4)
β blocker + ACE inhibitors	2 (1)
Cardiac + ACE inhibitors	4 (2)
Cardiac + other	9 (5)
ACE inhibitors + other antihypertensives	1 (1)
ACE inhibitors + other	3 (2)
Diuretic + β blocker + cardiac	3 (2)
Diuretic + β blocker + ACE inhibitors	3 (2)
Diuretic + β blocker + other antihypertensives	1 (1)
Diuretic + β blocker + other	4 (2)
Diuretic + cardiac + ACE inhibitors	3 (2)
Diuretic + cardiac + other antihypertensives	1 (1)
Diuretic + cardiac + other	6 (3)
Diuretic + ACE inhibitors + other	1 (1)
Diuretic + other antihypertensive + other	1 (1)
β blocker + cardiac + other	3 (2)
β blocker + ACE inhibitors + other	2 (1)
Cardiac + ACE inhibitors + other	2 (1)
Diuretic + β blocker + cardiac + other antihypertensive	1 (1)
Diuretic + β blocker + cardiac + other	8 (4)
Diuretic + β blocker + ACE inhibitors + other	1 (1)
Diuretic + β blocker + other antihypertensive + other	1 (1)
Total	189

ACE = angiotensin-converting enzyme inhibitors.

TABLE II Lipid* Data for All Hypertensive Patients (n = 213)—Those Receiving† (n = 189) and Not Receiving (n = 24) Drug Therapy for Hypertension

	Hypertensive Patients Not on Drug Therapy		Hypertensive Patients on Drug Therapy		All Hypertensive Patients	
	Baseline Mean	1-Month Change	Baseline Mean	1-Month Change	Baseline Mean	1-Month Change
Total cholesterol	273	−51‡	268	−52‡	268	−52‡
LDL cholesterol	195	−51‡	188	−52‡	189	−52‡
HDL cholesterol	47	2.5	43	2.9‡	43	2.8‡
Triglycerides	165	−21	194	−20‡	191	−20‡
Total/HDL	6.3	−1.4‡	6.6	−1.6‡	6.6	−1.6‡

*Unit for all lipid variables is mg/dl.
†Patients receiving antihypertensive, cardiac or other related medications.
‡Significant change from baseline (p level for matched pair *t* tests <0.0003).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

At baseline, mean total cholesterol ± SD was 268 ± 24 mg/dl, mean LDL cholesterol was 189 ± 22 mg/dl, mean HDL cholesterol was 43 ± 10 mg/dl, mean triglycerides was 191 ± 92 mg/dl, and mean ratio of total to HDL cholesterol was 6.6 ± 1.6.

Effectiveness at one month of therapy in all hypercholesterolemic hypertensive patients: Table II lists lipid values for all hypertensive patients at baseline and mean changes at 1 month from baseline. Figure 1 contains percent changes in serum lipids from baseline to 1 month of lovastatin therapy for all hypertensive patients.

In the hypertensive patients, total cholesterol decreased by 19% from a baseline mean of 268 mg/dl to a mean of 217 mg/dl after 1 month of therapy. LDL cholesterol was also reduced from 189 to 137 mg/dl, a 27% decrease. HDL cholesterol increased by 6%, from 43 to 46 mg/dl. Triglycerides were reduced by 10%, from 191 to 171 mg/dl; the ratio of total to HDL cholesterol decreased by 24%, from 6.6 to 5.0. All of these changes were significant (p = 0.0001).

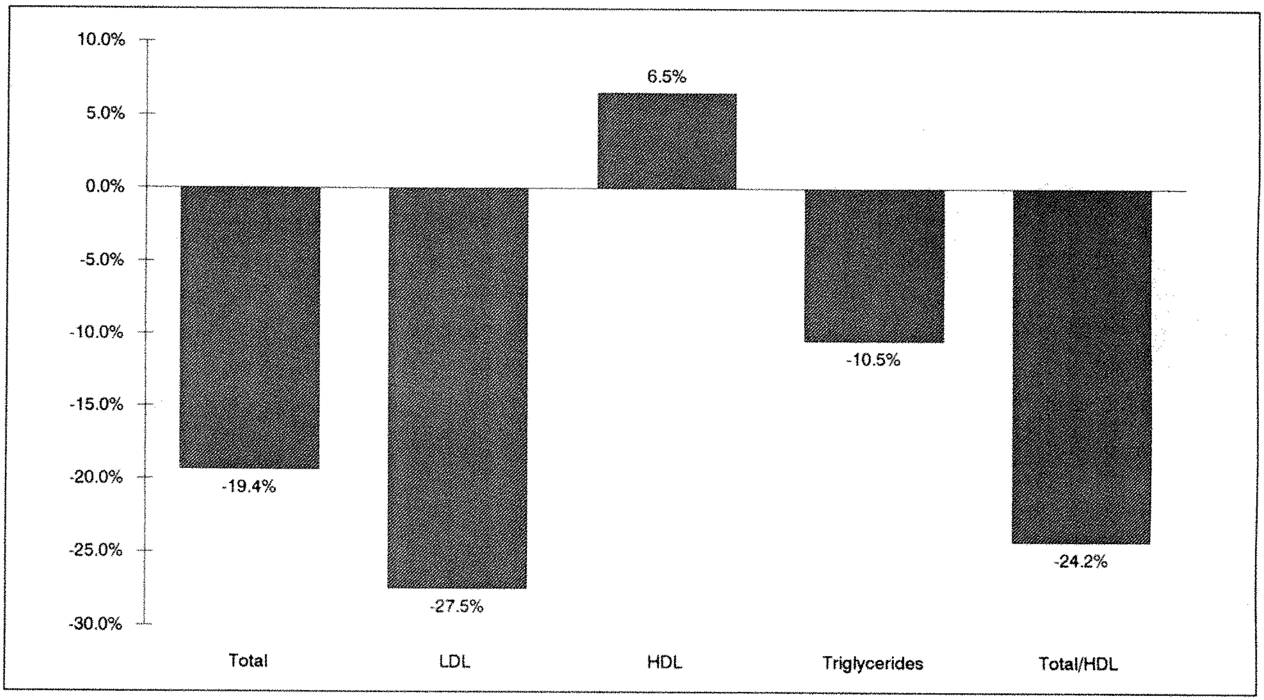

FIGURE 1. Percent changes from baseline for all hypertensive patients (n = 213). HDL = high-density lipoprotein; LDL = low-density lipoprotein.

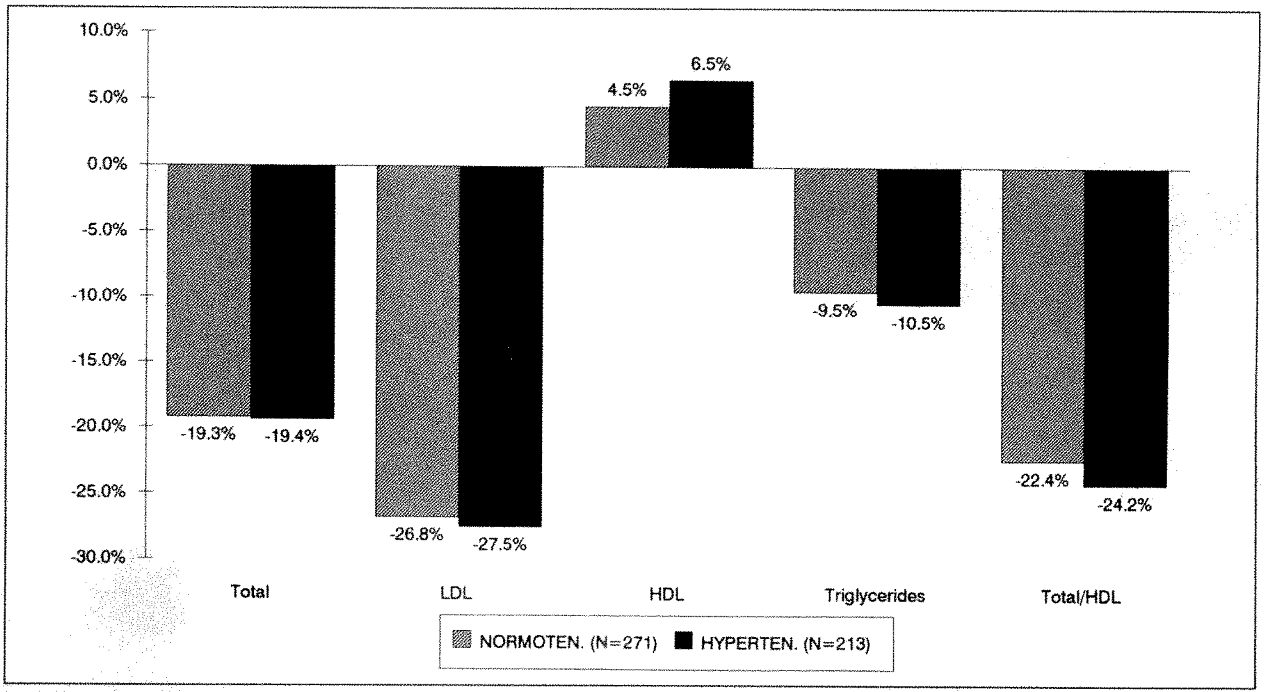

FIGURE 2. Percent changes from baseline for all hypertensive (HYPERTEN.) (n = 213) and normotensive (NORMOTEN.) (n = 271) patients. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

After 1 month of lovastatin therapy, 40% of hypertensive patients with coronary artery disease or 2 coronary artery disease risk factors (other than hypercholesterolemia) attained a goal LDL level (<130 mg/dl), whereas 67% of hypertensive patients who had neither coronary artery disease nor 2 risk factors attained goal LDL (<160 mg/dl). Overall, 42% of hypertensive patients achieved goal LDL levels; 47% of hypertensive patients who had baseline HDL <35 mg/dl achieved goal HDL levels (≥35 mg/dl).

Figure 2 represents the percent changes from baseline to 1 month of lovastatin therapy for all normotensive (n = 271) and hypertensive (n = 213) patients in the original study. As previously reported,[8] no significant differences were observed in lipid changes between the normotensive and hypertensive groups.

Effectiveness after one month of therapy by types of drug therapy: Table II also lists baseline mean lipid values and changes at 1 month from baseline for the 189 patients receiving drug therapy. The reason for the drug therapy was the patients' hypertension. The results of the analysis for this subgroup were almost identical to those of the total group of hypertensive patients. After 1 month of lovastatin therapy, total cholesterol and LDL cholesterol decreased by 19 and 28% respectively. HDL cholesterol increased by 7%. Triglycerides were reduced by 10% and the ratio of total to HDL cholesterol decreased by 24%. All changes were significant (p ≤0.0003). After 1 month of therapy, 43% of the patients in this subgroup achieved goal LDL levels. Forty-seven percent of patients in this subgroup who had a baseline HDL <35 mg/dl achieved desirable HDL levels (≥35 mg/dl) within 1 month of lovastatin therapy.

Table III contains mean lipid values at baseline and the mean of 1-month changes from baseline for the 163 patients receiving antihypertensive drugs. The results of the analysis for this subgroup were very similar to those of the total sample of hypertensive patients. After 1 month of therapy, total cholesterol, LDL cholesterol and triglycerides decreased by 19, 27 and 11%, respectively. HDL cholesterol increased by 7%. The ratio of total to HDL cholesterol was reduced by 24%. All changes were significant (p ≤0.0003). After 1 month of lovastatin therapy, 41% of the patients in this subgroup who had elevated baseline LDL cholesterol levels achieved goal LDL levels, whereas 47% of the patients with low baseline HDL cholesterol levels attained desirable HDL cholesterol levels.

TABLE III Lipid Data* for 163 Hypertensive Patients Receiving Antihypertensive Drugs (diuretics/beta blockers/angiotensin-converting enzyme inhibitors/other antihypertensive drugs)

	Baseline Mean	1-Month Change
Total cholesterol	268	−51†
LDL cholesterol	189	−51†
HDL cholesterol	42	3†
Triglycerides	197	−21†
Total/HDL	6.7	−1.6†

*Unit for all lipid variables is mg/dl.
†Significant change from baseline (p level for matched pair *t* tests <0.0003).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table IV contains separate analyses for the subgroups receiving diuretics, β blockers, and angiotensin-converting enzyme inhibitors. The results of the analyses for these subgroups were almost identical to those in the total group of hypertensive patients receiving antihypertensive medications. The only exception was the 1-month reduction in triglycerides, which was not statistically significant for the subgroups taking β blockers (n = 67) and angiotensin-converting enzyme inhibitors (n = 39). This may be attributed to the small sample sizes of these subgroups.

Six-month treatment period: The serum lipid reductions achieved after 1 month of diet plus lovastatin therapy were maintained over the full 6 months of treatment. Figure 3 plots mean values of LDL cholesterol during the 6 months of therapy for both hypertensive and normotensive patient groups. The trend observed in Figure 3 for LDL cholesterol is representative of the 6-month time course of the other lipid parameters which were examined but are not reported here. In all these parameters, change occurred after 1 month and was stable until the end of study.

By the end of the study, the average dosage for the hypertensive patient group was 35.8 ± 18.7 mg/day and that for the normotensive group was 38.6 ± 20.2 mg/day.

There were no unusual or unexpected adverse effects attributed to lovastatin during the 6-month treatment period. The most frequently reported adverse effects included abdominal pain, diarrhea and constipation. Overall, 85 patients reported at least 1 clinical adverse

TABLE IV Lipid Data* for Hypertensive Patients Receiving Diuretics (n = 102), Beta Blockers (n = 67) and Angiotensin-Converting Enzyme Inhibitors (n = 39)

	Diuretics		Beta Blockers		ACE Inhibitors	
	Baseline Mean	1-Month Change	Baseline Mean	1-Month Change	Baseline Mean	1-Month Change
Total cholesterol	271	−54†	265	−47†	268	−48†
LDL cholesterol	190	−52†	189	−51†	188	−50†
HDL cholesterol	42	3.5†	41	2.3†	42	2.8†
Triglycerides	211	−32†	195	−5.9	191	−5
Total/HDL	6.7	−1.7†	6.8	−1.5†	6.6	−1.5†

*Unit for all lipid variables is mg/dl.
†Significant change from baseline (p level for matched pair *t* tests <0.05).
ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

experience during the 6 months of diet plus lovastatin. Of these, 37 were hypertensive and 48 were normotensive patients. Thus, 17% of the hypertensive and 18% of normotensive group experienced at least 1 clinical adverse experience. The incidence and types of adverse effects in the hypertensive patients were no different from those of the normotensive patients.

Effectiveness after one month of lovastatin therapy by blood pressure categories: Patients with a diagnosis of hypertension were categorized into 6 diastolic blood pressure categories (≤74, 75 to 79, 80 to 84, 85 to 89, 90 to 94 and ≥94 mm Hg). Each patient was assigned to 1 of these categories initially based on baseline diastolic blood pressure, and again at 1 month after lovastatin treatment, now based on the 1-month diastolic blood pressure.

Figure 4 represents a plot of mean LDL cholesterol by diastolic blood pressure categories at baseline and at 1 month of lovastatin therapy. Plots of the other lipid parameters by diastolic blood pressure categories showed

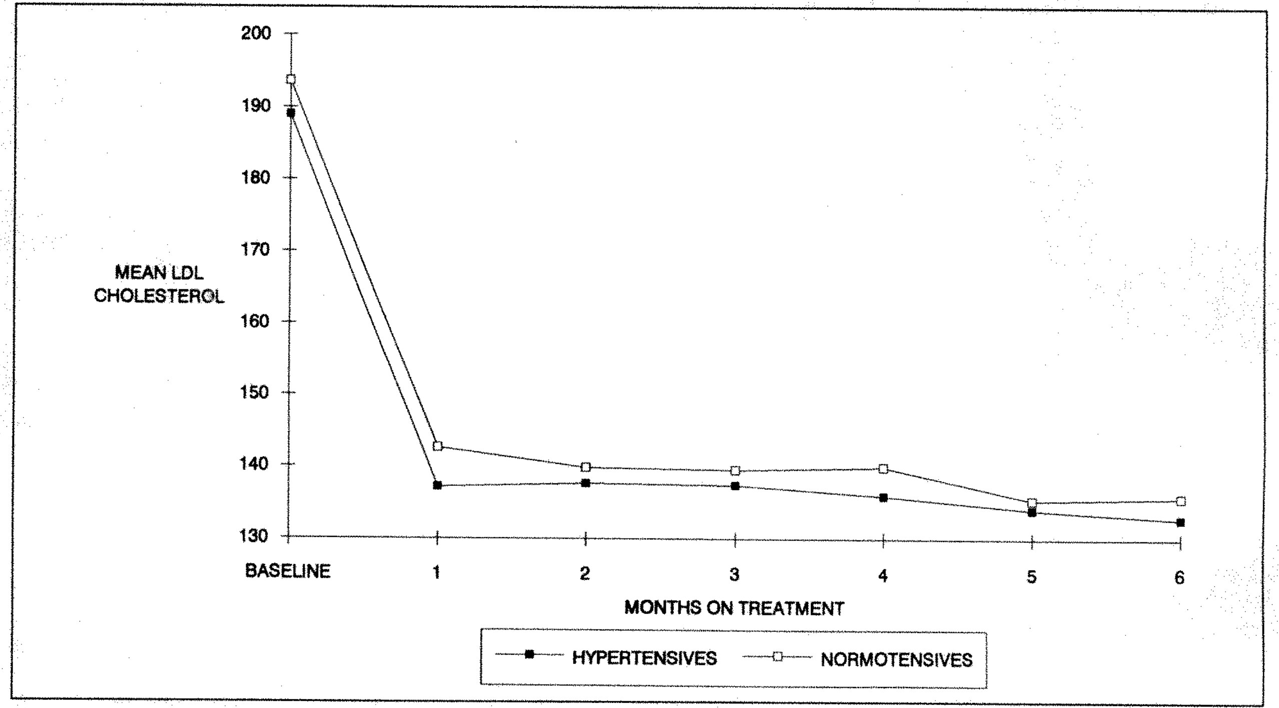

FIGURE 3. Low-density lipoprotein (LDL) cholesterol response to lovastatin treatment over 6 months for all hypertensive (n = 213) and normotensive (n = 271) patients.

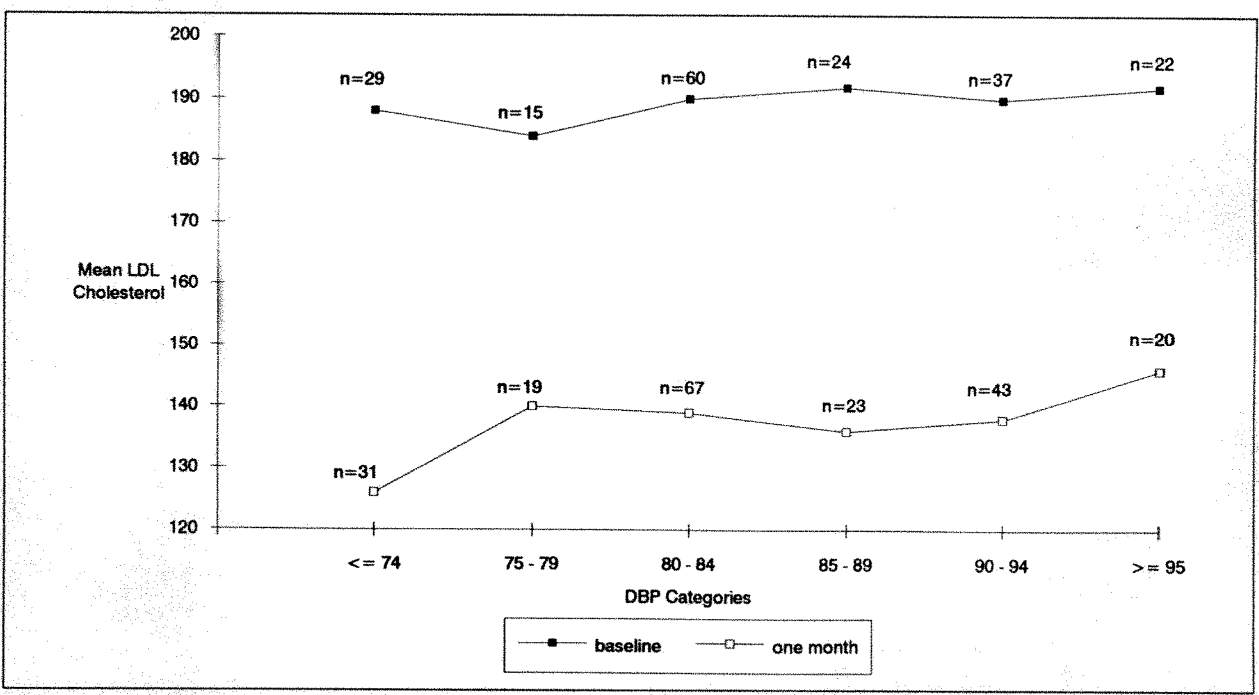

FIGURE 4. Mean low-density lipoprotein (LDL) cholesterol in hypertensive patients by diastolic blood pressure (DBP) categories at baseline and at 1 month of lovastatin therapy.

a pattern similar to that in Figure 4 and are not presented here. The improvements in lipids were independent of blood pressure levels.

DISCUSSION

Systemic hypertension tends to occur in association with lipid abnormalities.[6,7,9] These lipid abnormalities also accelerate the rate of atherogenesis associated with hypertension.[3] Some of the antihypertensive agents, while controlling hypertension, may lead to increases in LDL or triglycerides, or both, and reductions in HDL cholesterol.[6,9] This may have prevented the expected reduction in coronary artery disease risk anticipated from antihypertensive therapy.[5]

In some circumstances it is desirable to administer diuretics or β blockers to control hypertension (i.e., when hypertension is accompanied by cardiac failure or angina pectoris).[7] However, it is important to know whether a given antihypertension agent can adversely affect blood lipids. The present study showed that lovastatin therapy is effective in reducing serum lipids in hypercholesterolemic hypertensive patients without changes in blood pressure control. In our previous publication, we showed that reductions in serum lipids in hypertensive patients were comparable to those of normotensive patients.[8]

The dosage required to achieve substantial improvements in the lipid profile of hypertensive subjects (35.8 mg/day) was no greater than that needed for normotensive subjects (38.8 mg/day), nor were clinical adverse experiences more frequent. The desirable effect on lipids was obtained whether or not hypertension was being treated, and irrespective of the antihypertension agent used. Furthermore, improvements in lipids were obtained whether hypertension was mild or severe.

REFERENCES

1. Kannel WB. Hypertension and other risk factors in coronary heart disease. *Am Heart J* 1987;114:918–924.

2. Kannel WB. Risk factors in hypertension. *J Cardiovasc Pharmacol* 1989;13(suppl 1):S4–S10.

3. Chobanian AV. The influence of hypertension and other hemodynamic factors in atherogenesis. *Prog Cardiovasc Dis* 1983;26:177–196.

4. Middeke M, Holgrave H. Review of major intervention studies in hypertension and hyperlipidemia: focus on coronary heart disease. *Am Heart J* 1988;116:1708–1712.

5. Heyden S, Schneider KA, Fodir G. Coronary disease in hypertensives: a need to reduce cholesterol. *Int J Epidemiol* 1988;17:784–788.

6. Weinberger MH. Antihypertensive therapy and lipids: evidence, mechanisms and implications. *Arch Intern Med* 1985;145:1102–1105.

7. Kannel WB, Carter BL. Initial drug therapy for hypertensive patients with hyperlipidemia. *Am Heart J* 1989;118:1012–1021.

8. Kannel WB, D'Agostino RB, Stepanians MN, D'Agostino LC. Efficacy and tolerability of lovastatin in a six-month study: Analysis by gender, age, and hypertensive status. *Am J Cardiol* 1990;66:1B–10B.

9. McMahon SW, MacDonald GJ, Blacket BB. Plasma lipoprotein levels in treat ed and untreated hypertensive men and women. The National Heart Foundation of Australia risk factor prevalence study. *Arteriosclerosis* 1985;5:391–396.

Effects of Cardiac Transplantation on Endothelium-Dependent Dilation of the Peripheral Vasculature in Congestive Heart Failure

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Patients with congestive heart failure demonstrate attenuated endothelium-dependent vasodilation of the peripheral vasculature, but there are no data regarding the effect of therapies on this abnormality or whether this abnormality is reversible. This study was performed to address the hypothesis that abnormalities in endothelium-dependent vasodilation in heart failure are improved by heart transplantation. Forearm blood flow responses to the intraarterial administration of a dose range of methacholine, an endothelium-dependent vasodilator, and nitroprusside, an endothelium-independent vasodilator, were examined in 2 separate protocols. In protocol 1, forearm blood flow responses to methacholine in 14 heart transplant recipients were 5.02 ± 3.11, 11.55 ± 7.20 and 11.61 ± 10.24 ml/min/100 ml forearm volume. These responses were significantly greater than those in 10 patients with heart failure (2.23 ± 1.22, 4.60 ± 3.43 and 6.70 ± 4.91 ml/min/100 ml forearm volume; $p < 0.05$). In contrast, the responses to nitroprusside were nearly identical in the 2 groups. In protocol 2, six patients were studied before and 4 months (range 1 to 11) after transplantation. Methacholine responses before transplantation were 2.5 ± 1.3, 5.2 ± 1.5 and 7.3 ± 1.5 ml/min/100 ml forearm volume and were significantly improved after transplantation to 5.7 ± 1.2, 12.1 ± 3.0 and 14.2 ± 2.2 ml/min/100 ml forearm volume ($p < 0.05$). Peak reactive hyperemia responses increased significantly from 19.0 ± 3.7 to 44.8 ± 6.4 ml/min/100 ml forearm volume ($p < 0.01$) after transplantation. These data demonstrate that heart transplantation was associated with a significant improvement in the forearm blood flow responses to methacholine. The effect of heart transplantation was consistent when comparing a group of transplant recipients and patients with heart failure and in a separate group of patients studied both before and after transplantation. The improvement in endothelium-dependent vasodilation may occur in the setting of an improvement in overall responsiveness of the peripheral vasculature. These data demonstrate that abnormal endothelium-dependent responses in heart failure are reversible.

(Am J Cardiol 1993;71:88–93)

Data from both animal and human studies demonstrate that endothelium-dependent vasodilation is abnormal in a number of disease states characterized by vascular pathology and/or heightened vasoconstriction including atherosclerosis, hypercholesterolemia and systemic hypertension.[1–6] Other animal studies have shown that these abnormalities are reversible with dietary fish oil,[7] supplementation of L-arginine[8] or certain vasodilating agents.[9] Studies in a canine model of heart failure induced by rapid ventricular pacing and in the rat myocardial infarction model have also demonstrated abnormal endothelium-dependent vasodilation in the peripheral vessels.[10,11] There have been few studies assessing endothelial function in patients with heart failure. Treasure et al[12] found abnormal endothelium-dependent dilation of the coronary arteries in patients with dilated cardiomyopathy. We have previously demonstrated that forearm blood flow responses in patients with heart failure to endothelium-dependent vasodilators were reduced compared with responses to endothelium-independent vasodilators.[13] Our previous study additionally demonstrated that this abnormality was not related to age or the presence of atherosclerosis because the defect was of similar magnitude between patients with ischemic and idiopathic dilated cardiomyopathy. There are no data regarding the effect of therapies on endothelium-dependent vasodilator responses in patients with heart failure and whether or not this abnormality is reversible. Heart transplantation normalizes cardiac output and reverses excessive sympathetic stimulation and arterial baroreflex abnormalities.[14,15] We

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addressed the hypothesis that endothelium-dependent vasodilation of the peripheral vasculature in patients with heart failure could be improved by heart transplantation. We again used strain-gauge plethysmography to compare vasodilator responses to the intraarterial administration of subsystemic doses of methacholine in patients with heart failure before and after heart transplantation. We also compared the responses to nitroprusside, an endothelium-independent vasodilator, between heart transplant recipients and patients with heart failure.

TABLE I Patient Characteristics — Protocol 1

	Transplant Recipients (n = 14)	Patients with Heart Failure* (n = 10)
Age (year)	54 ± 9	54 ± 17
Heart rate (beats/min)	88 ± 13	85 ± 16
Blood pressure (mm Hg)	102 ± 12†	80 ± 12
Forearm blood flow (ml/min/100 ml FAV)	3.39 ± 1.47	2.87 ± 2.11
Forearm vascular resistance (U)	32 ± 13	39 ± 17
Plasma renin activity (ng/ml/hour)	13 (9.2–63)	36 (9.4–70)
Plasma norepinephrine (pg/ml)	374 ± 166†	618 ± 269
Total cholesterol (mg/dl)	225 ± 47‡	185 ± 40
Reactive hyperemia (ml/min/100 ml FAV)	31 ± 16	24 ± 14

*Patients were included in a previous report identifying the abnormality in endothelium-dependent vasodilation in heart failure.[13]
†p ≤0.01; ‡p ≤0.05 versus heart failure.
Plasma renin activity is reported as median (interquartile range) and compared by Wilcoxon rank-sum tests.
FAV = forearm volume.

TABLE II Patient Characteristics — Protocol 2

	Before Transplant	After Transplant
Weight (kg)	77.1 ± 12.2	78.3 ± 13.4
Mean arterial pressure (mm Hg)	75 ± 5	98 ± 10§
Heart rate (beats/min)	74 ± 16	85 ± 10
Forearm blood flow (ml/min/100 ml FAV)	3.3 ± 1.1	3.7 ± 1.5
Forearm vascular resistance (U)	30.5 ± 11.1	37.0 ± 16.0
Plasma norepinephrine (pg/ml)	698 ± 478	240 ± 91†
Plasma renin activity (ng/ml/hour)	16.4 (3.8–322)	3.8 (2.0–8.0)*
Creatinine (mg/dl)	1.1 ± 0.1	1.3 ± 0.4
Total cholesterol (mg/dl)	194 ± 20	235 ± 62*
Low-density lipoproteins (mg %) (n = 3)	121 ± 6	123 ± 31
Pulmonary-edge pressure (mm Hg) (n = 5)	20 ± 12	11 ± 3*
Cardiac output (L/min) (n = 5)	3.9 ± 0.8	5.2 ± 0.8*
Systemic vascular resistance (dynes s cm^{-5}) (n = 5)	1,585 ± 385	1,519 ± 353
Reactive hyperemia (ml/min/100 ml FAV)	19.0 ± 3.7	44.8 ± 6.4‡

$*0.05 < p < 0.10$; $†p < 0.05$; $‡p < 0.01$; $§p < 0.001$.
FAV = forearm volume.

METHODS

This study consisted of 2 protocols involving separate patient groups. Protocol 1 comprised 14 heart transplant recipients, including 13 men and 1 woman (mean age 54 ± 9 years) (Table I). Patients were studied an average of 14 months after transplantation (range 2 to 50 months) and were treated with cyclosporine, azathioprine and prednisone.[16] Antihypertensive therapy with enalapril (n = 2), captopril (n = 2), nifedipine (n = 4), and the combination of enalapril and nifedipine (n = 2) was withdrawn 24 to 48 hours before the study. For comparison, Table I also includes baseline characteristics of 10 patients with heart failure who were reported previously in a study demonstrating that endothelium-dependent vasodilation is abnormal in patients with heart failure.[13] These patients had moderate to severe left ventricular dysfunction (mean ejection fraction 20 ± 10%). All were clinically stable without acute decompensations and had New York Heart Association class II or III symptoms.

To further study the effects of transplantation, methacholine responses were examined in 6 male patients both before and after heart transplantation in protocol 2 (Table II). Mean age was 47 years (range 40 to 56). Before transplantation all patients had severe left ventricular systolic dysfunction with a mean ± SD ejection fraction of 25 ± 11% measured by radionuclide ventriculogram. Patients were clinically stable without acute decompensations of heart failure. Heart failure was related to ischemic heart disease (n = 3) or idiopathic dilated cardiomyopathy (n = 3). All patients were treated with digoxin and diuretics which were held on the morning of the study. Vasodilating therapy with converting enzyme inhibitors in all 6 patients was withdrawn 24 to 48 hours before the study. Patients were studied a second time an average of 4 months (range 1 to 11) after transplantation while receiving the same immunosuppression protocol used in protocol 1. The length of time between studies was 13 ± 4 months. Three patients were taking antihypertensive therapy after transplantation with either enalapril, nifedipine or isordil, which were withdrawn 24 to 48 hours before the study. All patients gave informed consent and this study was approved by the Committee on Human Subjects in Research.

The study preparation has been described previously.[13] An 18 gauge cannula was placed into the brachial artery of the nondominant arm for drug infusion using a Harvard infusion pump. Forearm blood flow was measured using a mercury in Silastic strain gauge and an electronically calibrated plethysmograph (Hokanson EC5). Five consecutive measurements were averaged and expressed as ml/min/100 ml forearm volume. Hand circulation was excluded with a wrist cuff inflated to suprasystolic pressure. Heart rate (beats/min) was recorded using a precordial electrocardiographic lead. Blood pressure was recorded in the contralateral arm with a cuff sphygmomanometer. Mean blood pressure (mm Hg) was calculated as the sum of the diastolic pressure and 1/3 of the pulse pressure. Peak reactive hyperemia was measured after 5 minutes of arterial occlusion produced by inflating the upper arm cuff to suprasystolic pressures. The first 2 flow measurements after cuff release were averaged.

Methacholine was used to stimulate endothelium-dependent vasodilation. Although methacholine has several pharmacologic actions, previous studies have demonstrated that its vasodilator action is attenuated by removal of the endothelium and by methylene blue but not by phentolamine or acetylsalicylic acid, suggesting that its predominant effect was endothelium-dependent.[1,5,17,18] Methacholine was reconstituted from a sterile lyophilized powder, passed through a 0.22 μ millipore filter and diluted in 5% dextrose in water. Based on our previous studies 3 doses were used including 0.3, 1.5 and 3.0 μg/min.[13] Nitroprusside was used as the reference endothelium-independent vasodilator. Although nitroprusside may produce vasodilation through hyperpolarization of vascular smooth muscle similar to endothelium-derived relaxing factor, this mechanism is less important than its direct activation of smooth muscle guanylate cyclase.[19] Nitroprusside was infused at doses of 1, 5 and 10 μg/min, since previous studies demonstrated that forearm blood flow responses were similar to those observed with methacholine in normal subjects.[13] The volumetric rate for all infusions was either 0.5 or 1 ml/min, which has only a small effect on forearm blood flow.[13]

After catheter placement, the subjects rested quietly for ≥30 minutes before baseline measurements. A second measurement was repeated after 5 minutes to insure a stable baseline. Blood samples were then obtained for baseline plasma renin activity and plasma norepinephrine. Peak reactive hyperemia was then measured followed by a 15-minute recovery period.

For protocol 1, forearm blood flow was measured before each infusion and then repetitively during a 1.5-minute infusion of each dose of methacholine. Because previous studies demonstrated that forearm blood flow remained constant during a 5-minute infusion of methacholine,[13] the last 5 flow measurements were averaged for all interventions. To monitor systemic effects, heart rate and blood pressure from the contralateral arm were recorded before and just before completion of the infusion. There was a 10- to 15-minute rest period between each dose of methacholine to allow flow to return to baseline. After 30 minutes, each subject then received a dose range of nitroprusside, again with each dose separated by 10 to 15 minutes.

In protocol 2, the response to an endothelium-dependent vasodilator was assessed before and after transplantation in the same patient. This included measurements of forearm blood flow at baseline and during the dose range of methacholine that was identical to protocol 1. The same protocol was completed after heart transplantation. Because of changes in the protocol, the first 2 patients received only the highest dose of methacholine instead of the full dose range. There was no overlap between patients included in protocols 1 and 2. Peak reactive hyperemia was measured both before and after trans plantation but nitroprusside responses were not measured.

Blood samples for plasma norepinephrine and plasma renin activity were analyzed by Dr. Ada Simon in the Cardiovascular Biochemistry Core Laboratory using a radioenzymatic technique with 8% intraassay coefficient of variation and radioimmunoassay, respectively.[20,21]

Baseline characteristics of the transplant recipients in protocol 1 were compared with the heart failure group by unpaired *t* test or Wilcoxon rank-sum test. Paired *t* tests or Wilcoxon signed rank tests were used to compare protocol 2 data before versus after transplantation. Analysis of variance with repeated measures was used to compare the methacholine and nitroprusside dose response curves in protocol 1. Since the methacholine responses in the heart transplant recipients from protocols 1 and 2 were similar, their responses were pooled to examine factors that relate to the variability in methacholine responses. Correlations with the responses to the 1.5 μg/min dose were examined for age, cholesterol, mean blood pressure, baseline forearm blood flow, neurohormonal measurements and time from transplantation. Data are expressed as mean ± 1 SD unless specified and are considered significant at $p < 0.05$.

RESULTS

The baseline characteristics of the 2 groups in protocol 1 are listed in Table I. Mean blood pressure was sig-

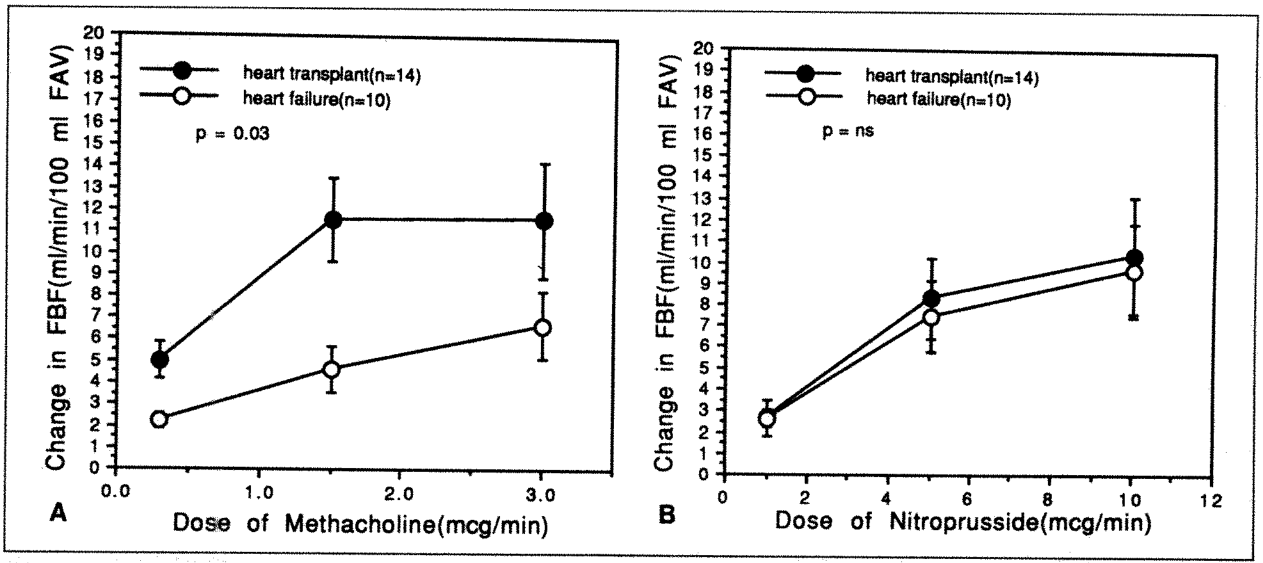

FIGURE 1. Forearm blood flow (FBF) responses to methacholine *(A)* and nitroprusside *(B)* in heart transplant recipients *(closed circles)* and patients with heart failure *(open circles)* from protocol 1. The methacholine responses were significantly increased in the transplant recipients compared to patients with heart failure. However, there were no significant differences in the nitroprusside responses between the 2 groups. Data are expressed as mean ± SE. FAV = forearm volume.

nificantly higher in the transplant recipients than in patients with heart failure. There were no significant differences in baseline forearm blood flow and forearm vascular resistance. When compared with patients with heart failure, transplant recipients had a similar plasma renin activity, a lower plasma norepinephrine and a higher total cholesterol.

For the 3 doses of methacholine, the forearm blood flow responses in the heart transplant recipients were 5.02 ± 3.11, 11.55 ± 7.20 and 11.61 ± 10.24 ml/min/100 ml forearm volume (Figure 1A). These responses were significantly increased compared with the patients with heart failure (2.23 ± 1.22, 4.60 ± 3.43 and 6.70 ± 4.91 ml/min/100 ml forearm volume; p = 0.03). To assess the specificity of this difference, responses to nitroprusside and peak reactive hyperemia were examined. For the 3 doses of nitroprusside, the increases in forearm blood flow for the heart transplant group were 2.64 ± 2.18, 8.32 ± 4.86, and 10.41 ± 6.45 ml/min/100 ml forearm volume and were nearly identical to the patients with heart failure (Figure 1B). Peak reactive hyperemia (Table I) tended to be higher in the transplant group (31 ± 16 vs 24 ± 14 ml/min/100 ml forearm volume; p = 0.10).

Table II summarizes the changes before and after transplantation in the 6 patients in protocol 2. After transplantation, mean blood pressure was significantly increased from 75 ± 5 to 98 ± 10 mm Hg (p <0.001). Weight, heart rate, forearm blood flow and forearm vascular resistance tended to increase, but the changes were not statistically significant. After transplantation, there was a significant decrease in plasma norepinephrine, a trend for a decrease in plasma renin activity and the expected improvements in pulmonary wedge pressure and cardiac output. Total cholesterol tended to increase but there was no change in low-density lipoproteins.

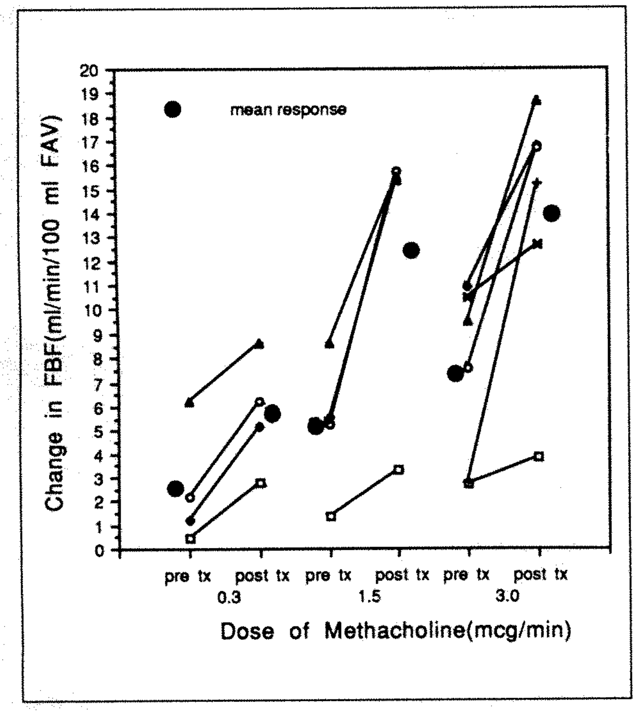

FIGURE 2. Individual and mean forearm blood flow (FBF) responses to methacholine in 6 patients both before and after transplantation (tx) from protocol 2. After transplantation, responses to all 3 doses of methacholine were significantly improved. FAV = forearm volume.

Before transplantation, the dose range of 0.3, 1.5 and 3.0 μg/min methacholine increased flow by 2.5 ± 1.3, 5.2 ± 1.5 and 7.3 ± 1.5 ml/min/100 ml forearm volume, respectively (Figure 2). After transplantation, these responses were significantly increased to 5.7 ± 1.2, 12.1 ± 3.0 and 14.2 ± 2.2 ml/min/100 ml forearm volume. The responses were consistent so that the changes were significant for all 3 doses (each p <0.05). Peak reactive hyperemia (Table II) was reduced to 19.0 ± 3.7 ml/min/100 ml forearm volume before transplantation and increased significantly to 44.8 ± 6.4 ml/min/100 ml forearm volume (p <0.01) after transplantation.

There were no changes in mean arterial pressure during the infusions of methacholine and nitroprusside in protocols 1 and 2. Therefore, changes in forearm vascular resistance were the inverse of changes in forearm blood flow and revealed similar findings. There was a trend for a higher baseline forearm blood flow in transplant recipients than in patients with heart failure in both protocols 1 and 2, but these differences were not significant. Nonetheless, analysis of the flow responses using analysis of covariance to adjust for baseline differences yielded similar results. Finally, similar to our previous analysis, the etiology of heart failure did not effect the abnormal response to methacholine in the patients with heart failure in either protocol 1 or 2, since similar responses were observed in patients with ischemic heart disease and patients with idiopathic dilated cardiomyopathy.

To assess potential mechanisms for the improvement in endothelium-dependent vasodilation after transplantation, the methacholine responses in the total of 20 transplant recipients from protocols 1 and 2 were examined relative to several factors. There were no significant correlations between the methacholine response and age (r = 0.32), cholesterol (r = –0.17) or plasma norepinephrine

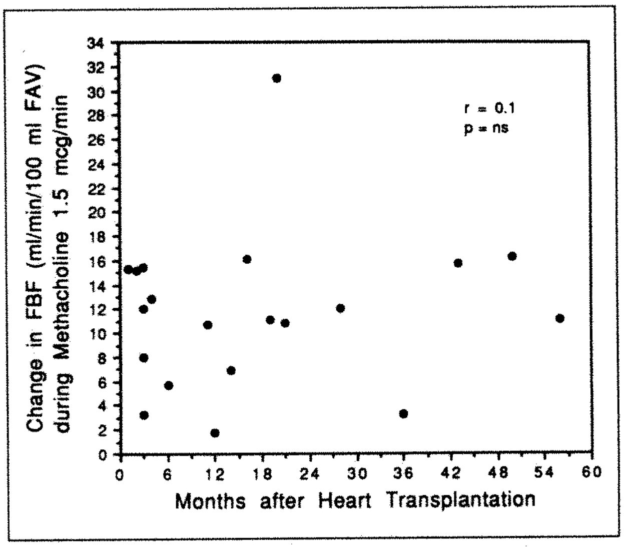

FIGURE 3. Correlation between forearm blood flow (FBF) response to the 1.5 μg/min dose of methacholine and time from transplantation in 20 heart transplant recipients. Normalization of the methacholine response was not dependent on time and was seen as early as 5 weeks after transplantation. FAV = forearm volume.

(r = −0.12). There were tendencies for associations between the methacholine response and baseline mean arterial pressure (r = 0.42; p = 0.07) and plasma renin activity (r = −0.43; p = 0.07). The methacholine response was significantly related to baseline forearm blood flow (r = 0.59, p = 0.01) so that the higher the baseline flow, the larger the methacholine response. Figure 3 summarizes the individual responses to the 1.5 μg/min dose of methacholine based on the time from transplantation. Improvement in the methacholine response was not dependent on time from transplantation (r = 0.1) and was seen as early as 5 weeks after transplantation.

DISCUSSION

These data demonstrate that heart transplantation was associated with a significant improvement in forearm blood flow responses to intraarterial methacholine. This improvement was identified when comparing a group of transplant recipients and patients with heart failure as well as comparing the same patient before and after transplantation, and was of similar magnitude in both comparisons. Although these data demonstrate an improvement in endothelium-dependent vasodilation after transplantation, we cannot exclude improvements in overall vascular responsiveness. In protocol 1, responses to nitroprusside were nearly identical between the heart failure and transplant groups. However, in protocol 2 peak reactive hyperemia responses were significantly higher after transplantation, confirming the findings of Sinoway et al.[22] Therefore, the improvement in endothelium-dependent vasodilation after transplantation may occur in the setting of an improvement in overall responsiveness of the peripheral vasculature.

Improvement in methacholine responses occurred despite potentially important differences in baseline characteristics between transplant recipients and patients with heart failure in protocol 1 and the comparison before and after transplantation in protocol 2. Specifically, the transplant recipients had increased blood pressure, treatment with cyclosporine, increased cholesterol and treatment with calcium antagonists. Endothelium-dependent vasodilation is attenuated in both animal models and patients with hypertension.[1,5] Studies have shown that cyclosporine results in vasoconstriction, possibly mediated by sympathetic stimulation or sodium retention.[23] Elevated cholesterol has been shown to limit endothelium-dependent responses in both animal models and human subjects.[1,4] Finally, calcium channel antagonists may by themselves have an inhibitory effect on endothelium-dependent responses.[24,25] Although the transplant recipients and patients with heart failure have several different baseline characteristics, all of these factors would be expected to reduce endothelium-dependent vasodilation after transplantation. Thus, improvements in the methacholine responses noted in the transplant recipients relative to the patients with heart failure are even more striking.

To our knowledge, this is the first study demonstrating improvement in endothelium-dependent vasodilator responses in the peripheral vasculature of patients with heart failure after heart transplantation. Endothelium-dependent coronary vasodilation is also abnormal in patients with heart failure[3,12] and frequently remains abnormal after transplantation.[26] This defect in the coronary arteries after transplantation is likely related to an immunologic process directed at donor endothelial cells. Thus, although endothelium-dependent vasodilation is abnormal in both the coronary and peripheral vasculature in patients with heart failure, there may be an important dissociation in these vascular beds after transplantation.

The demonstration that abnormal endothelium-dependent vasodilation in heart failure was improved by transplantation suggests that this defect is not irreversible and provides insight regarding possible pathophysiologic mechanisms. These data again suggest that age cannot account for attenuated endothelium-dependent vasodilation in heart failure. In protocol 1, the age of the transplant recipients was similar to the patients with heart failure. In protocol 2, the methacholine responses were increased in the transplant recipients despite being, on average, 1 year older. It is possible that the abnormality in heart failure and the improvement after transplantation are related to the effect of counterbalancing vasoconstriction mediated by neurohormonal pathways since both plasma norepinephrine and plasma renin activity were decreased after transplantation. However, the correlations between the methacholine response and plasma renin activity (r = −0.43) and plasma norepinephrine (r = −0.12) were modest. Additional studies are necessary to assess the specific influences of these neurohormonal mechanisms on methacholine responses. Early improvement and lack of correlation with time after transplantation suggest that changes in heart failure are related to a functional impairment. However, because we did not measure responses serially in the same patient after transplantation, we cannot exclude an effect mediated by structural changes or long-term remodeling of the vasculature.

This study is limited by the fact that patients in protocol 2 did not receive nitroprusside before and after transplantation so that a direct comparison of endothelium-independent responses with the patients as their own controls was not possible. Therefore, we cannot exclude a concomitant improvement in endothelium-independent vasodilation. However, the responses to nitroprusside in patients with heart failure and heart transplant recipients (protocol 1) were nearly identical. Methacholine responses are only indirect measurements of endothelium-dependent vasodilation, because in vitro methacholine has a direct smooth muscle constrictor effect, can inhibit norepinephrine release from nerve terminals and can stimulate prostacyclin production.[1,17,18] However, similar forearm studies have shown that acetylcholine responses are not altered by phentolamine or acetylsalicylic acid, suggesting that these other potential mechanisms do not contribute substantially to its vasodilator effects in vivo.[5] Patients with heart failure were all treated with digoxin. Ouabain has been shown in vitro to attenuate endothelium-dependent vasodilation in some vascular beds[27,28] but not in others.[29] Moreover, ouabain may also affect endothelium-independent vasodilation.[30] Additional studies are necessary to exclude a specific effect of digoxin in vivo.

This study was not designed to determine the specific mechanisms by which transplantation improved the methacholine responses. Some possibilities include an effect related to conditioning, increased cardiac output, withdrawal of vasoconstrictor tone or decreased vascular and interstitial edema. Finally, these studies evaluated stimulated endothelium-dependent responses so that the contributions to basal vasomotor tone are not known. It is conceivable that patients with heart failure have attenuated responses to stimulation by methacholine but have heightened basal release of endothelium-derived relaxing factor.

Acknowledgment: We would like to thank Jay N. Cohn, MD, for his continued advice and support during the performance of these studies. We also thank Susan Holmer, RN, Sofia Ormaza, RN, Ann Antolik, RN, Mary O'Rourke, RN, and Rebecca Diekmann, RN, for their assistance in the care of the patients with heart failure and transplant recipients included in this study.

REFERENCES

1. Vanhoutte PM. Endothelium and control of vascular function. State of the art lecture. *Hypertension* 1989;13:658–667.

2. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373–382.

3. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz P. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986;315:1046–1051.

4. Creager MA, Cooke JP, Mendlsohn ME, Gallagher SJ, Coleman SN, Loscalzo J, Dzau V. Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *J Clin Invest* 1990;86:228–234.

5. Panza JA, Quyyumi AA, Brush JE, Epstein SE. Abnormal endothelium dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990;323:22–27.

6. Luscher TF, Richard V, Tschudi M, Yang Z, Boulanger L. Endothelial control of vascular tone in large and small coronary arteries. *J Am Coll Cardiol* 1990; 15:519–527.

7. Shimokawa H, Vanhoutte PM. Dietary cod liver oil improves endothelium-dependent responses in hypercholesterolemic and atherosclerotic porcine coronary arteries. *Circulation* 1988;78:1421–1430.

8. Girerd XJ, Hirsch AT, Cooke JP, Dzau VJ, Creager MA. L-arginine augments endothelium-dependent vasodilation in cholesterol fed rabbits. *Circ Res* 1990; 67:1301–1308.

9. Schultz PJ, Raij L. Effects of antihypertensive agents on endothelium dependent and endothelium independent relaxation. *Br J Clin Pharm* 1989;28:1515–1525.

10. Kaiser L, Spickard RC, Olivier NB. Heart failure depresses endothelial cell dependent relaxation to acetylcholine in canine femoral artery. *Am J Physiol* 1989; 256:H962–H967.

11. Ontkean MT, Gay RG, Greenberg BH. Diminished endothelium derived relaxing factor activity in an experimental model of chronic heart failure. *Circ Res* 1991;69:1088–1096.

12. Treasure CB, Vita JA, Cox DA, Fish RD, Gordon JB, Mudge GH, Colucci WS, Sutton MG, Selwyn AP, Alexander RW, Ganz P. Endothelium dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. *Circulation* 1990;81:772–779.

13. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium dependent vasodilation is attenuated in patients with heart failure. *Circulation* 1991; 84:1589–1596.

14. Levine TB, Olivari MT, Cohn JN. Effects of orthotopic heart transplantation on sympathetic control mechanisms in congestive heart failure. *Am J Cardiol* 1986;58:1035–1040.

15. Ellenbogen KA, Mohanty PK, Szentpetery S, Thames MD. Arterial baroreflex abnormalities in heart failure: reversal after orthotopic cardiac transplantation. *Circulation* 1989;79:51–58.

16. Olivari MT, Kubo SH, Braunlin EA, Bolman RM, Ring WS. Five year experience with triple drug immunosuppressive therapy in cardiac transplantation. *Circulation* 1990;82(suppl IV):IV-276–IV-280.

17. Angus JA, Campbell GR, Cocks TM, Manderson M. Vasodilation by acetylcholine is endothelium-dependent. A study of sonomicrometry in canine femoral artery in vivo. *J Physiol* 1983;34:201–222.

18. Forstermann U, Mulsch A, Bohme E, Busse R. Stimulation of soluble guanylate cyclase by an acetylcholine-induced endothelium-derived factor from rabbit and canine arteries. *Circ Res* 1986;58:531–538.

19. Martin W, Villani GM, Jothianandan D, Furchgott GF. Selective blockade of endothelium dependent and glyceryl trinitrate induced relaxation by hemoglobin and by methylene blue in the rabbit aorta. *J Pharmacol Exp Ther* 1985;232:708–716.

20. Passon PG, Peuler JD. A simplified radiometric assay for norepinephrine and epinephrine. *Anal Biochem* 1973;51:618–631.

21. Sealey JE, Gerten-Banes J, Laragh JH. The renin system: variations in man measured by radioimmunoassay or bioassay. *Kidney Int* 1972;1:240–253.

22. Sinoway LI, Minotti JR, Davis D, Pennock JL, Burg JE, Musch TI, Zelis R. Delayed reversal of impaired vasodilation in congestive heart failure after heart transplantation. *Am J Cardiol* 1988;61:1076–1079.

23. Kahan BD. Cyclosporine. *N Engl J Med* 1989;321:1725–1738.

24. Winquist RJ, Bunting PB, Schofield TL. Blockade of endothelium-dependent relaxation by the amiloride analog dichlorobenzamil: possible role of Na^+/Ca^{++} exchange in the release of endothelium-derived relaxant factor. *J Pharm Exp Ther* 1985;235:655–660.

25. Singer HA, Peach MJ. Calcium and endothelial mediated vascular smooth muscle relaxation in rabbit aorta. *Hypertension* 1982;4(suppl II):19–25.

26. Fish RD, Nabel EG, Selwyn AP, Ludmer PL, Mudge GH, Kirschenbaum JM, Schoen FJ, Alexander RW, Ganz P. Responses of coronary arteries of cardiac transplant patients to acetylcholine. *J Clin Invest* 1988;81:21–31.

27. Rapoport RM, Schwartz K, Murad F. Effects of Na K^+ pump inhibitors and membrane depolarizing agents on acetylcholine induced endothelium dependent relaxation and cyclic GMP accumulation in rat aorta. *Eur J Pharmacol* 1985; 110:203–209.

28. Woolfson RG, Poston L. Effect of ouabain on endothelium-dependent relaxation of human resistance arteries. *Hypertension* 1991;17:619–625.

29. Suzuki H. The electrogenic Na^-K pump does not contribute to endothelium-dependent hyperpolarization in the rabbit ear. *Eur J Pharmacol* 1988;156:295–297.

30. Rapoport RM, Schwartz K, Murad F. Effect of sodium potassium inhibitors and membrane-depolarizing agents on sodium nitroprusside induced relaxation and cyclic guanosine monophosphate accumulation in rat aorta. *Circ Res* 1985;57: 164–170.

MISCELLANEOUS

Atrioventricular Conduction in Children of Women with Systemic Lupus Erythematosus

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Janet Ellsworth, MD, Donita B. Sullivan, MD, and Aaron M. Stern, MD

The neonatal lupus syndrome consists of transient cutaneous lupus lesions or permanent congenital complete heart block (or hepatic fibrosis), or both, in infants born to mothers with systemic lupus erythematosus (SLE). The frequency of conduction abnormalities was examined in 86 offspring of 53 women affected by SLE. Electrocardiograms from the offspring demonstrated normal sinus rhythm in 84 of 86 offspring. The PR interval was normal for age (<95th percentile) in 82 offspring and normal for heart rate in 81. Three children had a PR interval >95th percentile (i.e., first-degree heart block) for both age and heart rate. The PR interval of the other 6 subjects with first-degree heart block for age or heart rate (≥95th percentile) was ≤0.18 second. In contrast, using a rank assignment of PR intervals in relation to heart rate and age derived from published standards, grouped data indicated that heart rate adjusted for age was greater and PR interval adjusted for heart rate longer in offspring of mothers who had the onset of SLE before or during pregnancy than in the normal population; this observation did not hold for offspring whose mothers developed SLE after the pregnancy. These findings indicate that offspring of mothers with SLE, even in the absence of an abnormal electrocardiogram, may have experienced a maternal internal environment that produces subclinical changes in atrioventricular conduction. However, newborns with a normal pulse rate are unlikely to have significant abnormalities in atrioventricular conduction and do not need screening electrocardiograms at birth.

(Am J Cardiol 1993;71:94–98)

The neonatal lupus syndrome consists of transient cutaneous lupus lesions or permanent congenital complete heart block (or hepatic fibrosis), or both, occurring in a small percentage of infants born to mothers with systemic lupus erythematosus (SLE). The prevalence of connective tissue disease in mothers of babies with congenital complete heart block ranges from 33 to 64%.[1,2] Half of these women are symptomatic; the other half have only serologic evidence of connective tissue disease.[3] In symptomatic mothers, SLE is the usual underlying disorder, but Sjogren syndrome, rheumatoid arthritis and undifferentiated connective tissue disease have also been found.[2,4,5] In 1 study, the relation between maternal high-titer antibody and congenital complete heart block suggested a possible dose-response effect.[6] However, the electrocardiograms of all the infants were not reported. Support for a dose-response relation would be increased, if more subtle conduction disturbances were detected by the electrocardiogram. This study examines the frequency of conduction abnormalities in offspring of mothers with SLE by identifying mothers with SLE rather than by identifying affected infants. Our hypothesis is that offspring of mothers with SLE would have a spectrum of conduction disturbances on the resting electrocardiogram ranging from first-degree atrioventricular block to the already recognized congenital complete heart block.

METHODS

In 1982 and again in 1988, women with SLE (1982 American Rheumatism Association revised criteria for SLE) followed in the Rheumatology Clinic at the University of Michigan were asked at the time of their regularly scheduled appointment if they had ever been pregnant. For each cohort (1982 [n = 32] and 1988 [n = 21]), women with children were later contacted by telephone and asked to participate in the study. Thirty-two of 42 mothers contacted in 1982 and 21 of 22 in 1988 agreed to participate in the study. In all, 84 of 92 living offspring of 53 women were evaluated. Except for 3 siblings who had electrocardiograms obtained at a local hospital, electrocardiograms were recorded on a Cambridge VS-550 electrocardiographic recorder (frequency response, direct current to 100 Hz) with a heat writer on paper moving at 50 mm/s. Consent forms and questionnaires pertaining to the mother's and child's medical history were completed for each offspring. Anti-SSA/Ro and Anti-SSb/La antibody status was available from 25 mothers (18 from 1988, and 7 from 1982). The study protocol, written

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consent forms and questionnaires for both cohorts were similar and were approved by the institutional review board of the University of Michigan.

Electrocardiographic intervals (Table I) (heart rate, and PR, QRS and QT intervals) were measured independently by 2 investigators using a ruler calibrated to 0.5 mm. Because electrocardiographic standards for children have been published, are widely accepted and are constant over time, a contemporary control group was not necessary. We used standards published in 1980 by Davignon et al[7] that were derived from data in a population of 2,141 children (age range 0 to 16 years) divided into 12 age groups. Age-dependent PR intervals and QRS duration percentiles, as well as distributions of

TABLE I Maternal Antibody Status and Offspring Electrocardiographic Data

						Electrocardiographic Intervals		
Mother	Ro-Ab	La-Ab	Offspring	Age (year)	HR (beats/min)	PR (ms)	QRS (ms)	QTNC (ms)
1	Neg	Neg	1A	14	91	130	70	340
			1B	11	92	160	80	320
2	Pos	Pos	2	17	85	120	80	320
3	Neg	Neg	3	2	115	110	80	280
4	Neg	Neg	4	3	101	160	80	320*
5	Pos	Pos	5	16	107	120	60	300
6	Pos	Neg	6	8	81	120	70	350
7	Pos	Neg	7	24	79	140	80	340
8	NA	NA	8	6	107	100	60	320
9	NA	NA	9A	12	64	160	80	340
			9B	15	58	160	100	400
			9C	14	58	90	100	440†
10	Neg	Neg	10A	6	100	170	100	300‡
			10B	9	65	130	60	340
			10C	12	75	150	70	360
11	Neg	Neg	11	6	97	120	80	320
12	Neg	Neg	12	6	64	120	80	360
13	Pos	Neg	13	3	143	130	60	260
14	Pos	Pos	14	15	65	140	80	360
15	Pos	Neg	15A	13	71	160	40	330
			15B	6	95	150	60	320
16	Neg	Neg	16	2	140	120	50	260
17	Neg	Neg	17	0.5	136	170	50	300‡
18	NA	NA	18A	28	98	160	70	330*
			18B	36	85	180	80	330*
			18C	39	88	160	60	360
19	Neg	Neg	19	13	79	140	80	350
20	Pos	Neg	20	6	89	110	50	300
21	Pos	Pos	21A	10	100	120	80	320
			22B	0.3	118	80	50	300§
22	NA	NA	22A	13	77	160	70	320
	NA	NA	22B	15	95	140	80	340
23	NA	NA	23	0.11	165	110	40	220
24	Neg	Neg	24	0.13	200	80	40	220
25	NA	NA	25A	13	83	140	60	360
			25B	20	75	140	100	370
26	NA	NA	26	4	75	120	60	320
27	NA	NA	27	3	100	140	80	320
28	NA	NA	28A	4	95	140	70	300
	NA	NA	28B	12	82	120	70	370
	NA	NA	28C	17	67	140	60	360
	NA	NA	28D	21	78	150	60	340
29	Neg	Neg	29A	15	70	150	90	380
	Neg	Neg	29B	12	67	130	80	400
	Neg	Neg	29C	9	65	160	80	380
30	NA	NA	30A	10	75	120	60	320
	NA	NA	30B	5	80	120	60	320
31	NA	NA	31A	11	60	120	70	380
32	Neg	Neg	32A	15	73	160	90	360
	Neg	Neg	32B	13	69	180	80	370‡
33	NA	NA	33A	11	105	130	60	300
	NA	NA	33B	10	67	140	60	370
	NA	NA	33C	9	107	120	70	300

*First-degree heart block for age or heart rate; †atrioventricular dissociation with junctional rhythm; ‡first-degree atrioventricular block for both age and heart rate; §short PR interval with no δ wave, suggesting enhanced atrioventricular conduction.

HR = heart rate; La-Ab = anti-La antibody; NA = not available; Neg = maternal antibody not detectable; Pos = maternal antibody present; PR = PR interval; Ro-Ab = anti-Ro antibody.

TABLE I (Cont'd)

						Electrocardiographic Intervals		
Mother	Ro-Ab	La-Ab	Offspring	Age (year)	HR (beats/min)	PR (ms)	QRS (ms)	QTNC (ms)
34	NA	NA	34A	22	60	160	80	360
	NA	NA	34B	26	75	180	60	360*
	NA	NA	34C	31	49	160	100	380
	NA	NA	34D	28	77	140	80	400
35	NA	NA	35A	14	75	140	60	360
	NA	NA	35B	7	80	120	80	360
36	NA	NA	36	24	74	160	80	400
37	NA	37A	36A	15	75	140	100	370
		37B	36B	14	75	160	100	330
38	NA	NA	38	7	72	120	60	300
39	NA	NA	39A	33	63	160	80	360
	NA	NA	39B	30	72	140	80	360
	NA	NA	39C	24	75	140	90	320
40	NA	NA	40	7	136	150	80	260
41	NA	NA	41A	20	86	150	70	330
	NA	NA	41B	23	63	160	60	340
	NA	NA	41C	25	88	140	50	320
42	Pos	Neg	42	31	75	160	80	370
43	Neg	Neg	43A	5	88	140	80	340
	Neg	Neg	43B	10	88	120	60	340
44	NA	NA	44	10	100	140	60	320
45	NA	NA	45	42	75	100	60	370
46	NA	NA	46A	11	70	120	80	380
	NA	NA	46B	12	68	120	60	400
47	Pos	Neg	47	14	96	140	80	360
48	NA	NA	48	32	70	150	60	340
49	Pos	Neg	49	28	77	140	70	360
50	NA	NA	50	12	114	160	60	310
51	NA	NA	51A	28	68	120	60	360
	NA	NA	51B	25	60	180	70	440
52	NA	NA	52A	14	75	130	90	320
	NA	NA	52B	17	53	160	90	380
53	NA	NA	53	20	100	140	70	320

*First-degree heart block for age or heart rate; †atrioventricular dissociation with junctional rhythm; ‡first-degree atrioventricular block for both age and heart rate; §short PR interval with no δ wave, suggesting enhanced atrioventricular conduction.

HR = heart rate; La-Ab = anti-La antibody; NA = not available; Neg = maternal antibody not detectable; Pos = maternal antibody present; PR = PR interval; Ro-Ab = anti-Ro antibody.

these values, from that study were used as the normative values in the present study. However, because of the wide range of normal PR intervals at different heart rates and ages (Figures 3 and 4 from Davignon et al),[7] each PR interval of the subjects in our study was assigned a rank order of 1 to 8 corresponding, in order, to a rank value <2nd percentile (rank value = 1), between the 2nd and 5th, the 5th and 25th, the 25th and 50th, the 50th and 75th, the 75th and 95th, and the 95th and 98th percentiles, and finally, >98th percentile (rank value = 8). The following 3 analyses were then performed: (1) comparison of the 1982 and 1988 data to determine if the cohorts differed; (2) comparison of all data to examine the effect of onset (before and during vs after pregnancy), as well as other variables; and (3) repetition of analysis 2 using only data from the eldest child to eliminate any intrafamily effects. Tests used to perform these analyses included 1-way analysis of variance model, Mann-Whitney nonparametric test, chi-square test of independence, and analysis of co-variance and log-linear models. Differences were considered significant if the p value was ≤0.05.

RESULTS

In this group of 53 women with SLE, serologic results were known for 25 (Table I). A woman was considered as having anti-SSA/Ro antibody if the antibody was found at any time. The rationale for this assumption is based on the reported occurrence of anti-SSA/Ro antibody before the onset of symptoms of SLE[3] and because this antibody tends to remain present over prolonged periods of time.[8] Of these 25 women, most (76%) were antinuclear antibody positive; 50% were anti-SSA/Ro antibody positive, and 56% were anti-SSB/La antibody positive. No mother had a child with congenital complete heart block.

The mean age of the offspring studied was 14.5 ± 9.5 years. One-way analysis showed that the 1982 cohort was older (p = 0.05) and, as would thus be expected, had a slower heart rate (p = 0.04) than did the 1988 cohort. However, the electrocardiographic intervals did not differ significantly between the 2 groups. SLE was diagnosed before or during pregnancy in 28 cases and after pregnancy in the remaining 58. During 7 pregnancies, the mothers were treated with prednisone.

Analysis of electrocardiographic data (Table I) showed sinus rhythm in 85 of 86 offspring. A 14-year-old male offspring had both intermittent atrioventricular dissociation and normal sinus rhythm, but normal atrioventricular conduction during sinus rhythm. Serologic data were not available from this subject's mother. One 20-year-old female offspring had right-axis deviation. The PR interval was <95th percentile for age (i.e., normal) in 82 of 86 offspring and <95th percentile for heart rate in 81. Three children had a PR interval >95th percentile (i.e., first-degree heart block) for both age and heart rate: A 6-month-old male had a PR interval of 0.17 seconds at a heart rate of 136 beats/min, a 6-year-old male had a PR interval of 0.17 second at a heart rate of 100 beats/min, and a 13-year-old male had a PR of 0.18 second at a heart rate of 69 beats/min. Although 2 of the mothers of these 3 subjects developed SLE before or during the pregnancy, all 3 mothers' serum was devoid of anti-SSA/Ro and anti-SSB/La antibody. The PR interval of the other 6 subjects with first-degree heart block for age or heart rate (i.e., ≥95th percentile) was ≤0.18 second. However, all offspring had intact atrioventricular conduction, and no other isolated electrocardiographic abnormalities were found.

In contrast to the individual data, grouped data suggested subtle effects of maternal SLE on atrioventricular conduction in offspring. Using the aforementioned rank assignment of PR intervals in relation to heart rate and age (and heart rate in relation to age), 2 differences were observed. First, heart rate adjusted for age was significantly ($p = 0.003$) higher in offspring whose mothers had the onset of SLE before or during pregnancy than in the normal population[7]; this difference was not present for children whose mothers developed SLE after pregnancy. Second, PR interval adjusted for heart rate (i.e., rank score indicating a difference in percentile level) was significantly ($p = 0.0001$) longer (i.e., score was greater) in offspring whose mothers developed SLE before or during pregnancy than in the normal population.[7] This difference was not present for subjects whose mothers developed SLE after pregnancy. These relations remained when only the eldest child was included in the analysis, supporting the likelihood of a difference related to SLE effects rather than to intrafamily effects. However, the data were insufficient to distinguish between the effects of age and onset of SLE (before and during vs after pregnancy) on PR interval. The analysis examining an antibody effect on PR interval produced no significant results, perhaps owing to a small number of women in whom antibody status was known.

DISCUSSION

In these 2 cohorts comprising 86 offspring of 53 mothers with SLE, we detected no isolated, significant, electrocardiographic abnormalities, even in children whose mothers were anti-SSA/Ro antibody positive. First-degree atrioventricular block was detected in 3 offspring; however, the 3 respective mothers were antibody negative during pregnancy, suggesting that in these cases the minor conduction abnormalities were probably unrelated to neonatal SLE. Similarly, the finding of an intermittent escape junctional rhythm in 1 adolescent offspring, as well as the right-axis deviation in another, probably represents a normal variant. However, the grouped data suggest that a subclinical effect of maternal SLE may be affecting the fetus and may contribute to a subtle delay in atrioventricular conduction in the fully developed infant or child.

Mechanism of neonatal systemic lupus erythematosus: Neonatal SLE syndrome is mediated by the transplacental passage (after the 12th to 16th week of gestation) of maternal immunoglobulin G antibodies to the fetus of a woman with SLE, followed by an immunologically-based inflammatory reaction (and/or deposition) of these antibodies with antigens of the fetal skin and heart, or both.[3,5,6,9–14] Anti-SSA/Ro and anti-SSB/La antibodies to soluble tissue ribonucleoprotein antigens found in the cytoplasm or nucleus of human cells, or both,[10] have been proposed as the etiologic agents of congenital complete heart block.[11] Demonstration of immunofluorescence from antibody deposition in cardiac tissue provides evidence that placentally transmitted immunoglobulin G antibodies may act directly on the heart, producing deposition at the atrioventricular node, central fibrous body and fibrous annulus.[15–19] Furthermore, Alexander et al[20] have demonstrated an antibody (anti-SSA/Ro and anti-SSB/La)-mediated inhibition of neonatal rabbit cardiac repolarization, indicating a direct effect on the electrophysiologic properties of developing excitable tissue. All these observations are compatible with a dose-response effect of maternal antibodies on immature atrioventricular conduction tissue.

Risk to fetus: In a retrospective study of offspring of women with SLE, Ramsey-Goldman et al[6] described 16 infants with congenital complete heart block in 96 pregnancies of women who had anti-SSA/Ro antibody. In contrast, only 1 infant in 235 pregnancies of women with SLE but without anti-SSA/Ro antibody had neonatal SLE. In that study, the overall risk of a woman with SLE having an infant with congenital complete heart block was estimated to be 1:60 (when corrected for referral bias), but the risk was considerably greater (1:20) if anti-SSA/Ro antibody was present. Buyon et al[21] have described maternal antibodies from the mothers of neonatal SLE infants to specific peptides of the ribonuclear SSA/Ro complex, as well as to the SSB/La particle; both of these peptides are abundant in fetal cardiac tissues. The presence of antibodies to these specific peptides increases the risk ratio of a mother with SLE giving birth to an infant with neonatal lupus by a factor of 35.

Clinical implications: The incidence, reduced morbidity and improved survival of women of childbearing age affected by SLE renders pregnancy in these cases an important clinical problem. This study was retrospective. Thus, transient conduction disturbances in the neonatal period may have been overlooked. However, the study underscores the strong possibility of subclinical alterations in atrioventricular conduction in some fetuses exposed to a maternal SLE environment, and thus supports a dose-response relation between atrioventricular conduction in the fetus and infant and maternal SLE antibodies. However, because of bradycardia noted in the newborn at birth, congenital high-grade or complete heart block is usually recognized and confirmed by electrocardiography. Thus, if the heart rate of a fetus or newborn whose mother has SLE is normal, neither early obstetric intervention nor routine postnatal electrocardiograms are necessary.

Acknowledgment: We wish to acknowledge and extend our thanks to MaryBeth Landrum and Morton Brown for statistical advice and support.

REFERENCES

1. Esscher E, Scott JS. Congenital heart block and maternal systemic lupus erythematosus. *Br Med J* 1979;1:1235–1238.

2. McCue CM, Mantakas ME, Tingelstad JB, Ruddy S. Congenital heart block in newborns of mothers with connective tissue disease. *Circulation* 1977;56:82–90.

3. Scott JS, Maddison PJ, Taylor PV, Esscher E, Scott O, Skinner RP. Connective-tissue disease, antibodies to ribonucleoprotein, and congenital heart block. *N Engl J Med* 1983;309:209–212.

4. Nolan RJ, Shulman ST, Victorica BE. Congenital complete heart block associated with maternal mixed connective tissue disease. *J Pediatr* 1979;95:420–422.

5. Chameides L, Truex RC, Vetter V, Rashkind WJ, Galioto FM, Noonan JA. Association of maternal SLE with congenital complete heart block. *N Engl J Med* 1977;297:1204–1207.

6. Ramsey-Goldman R, Horn D, Deng JS, Ziegler GC, Kahl LE, Steen VD, LaPorte RE, Medsger TA. Anti-SS-A antibodies and fetal outcome in maternal systemic lupus erythematosus. *Arthritis Rheum* 1986;29;10:1269–1273.

7. Davignon A, Rautaharju P, Boisselle E, Soumis F, Megelas M, Choquette A. Normal electrocardiogram standards for infants and children. *Pediatr Cardiol* 1979/1980;1:123–131.

8. Wasicek CA, Reichlin M. Clinical and serological differences between systemic lupus erythematosus patients with antibodies to Ro versus patients with antibodies to Ro and La. *J Clin Invest* 1982;69:835–843.

9. Provost TT, Watson R, Gammon WR, Radowsky M, Harley JB, Reichlin M. The neonatal lupus syndrome associated with U_1RNP (nRNP) antibodies. *N Engl J Med* 1987;316;18:1135–1138.

10. Kraft JE, Hardin JA. Linked sets of antinuclear antibodies: what do they mean? *J Rheumatol* 1987;14(suppl 13):106–109.

11. Harley JB, Kaine JL, Fox OF, Reichlin M, Gruber B. Ro(SS-A) antibody and antigen in a patient with congenital complete heart block. *Arthritis Rheum* 1985;28:1321–1325.

12. Harmon CE, Lee LA, Huff JC, Norris DA, Weston WL. The frequency of antibodies to the SS-A/Ro antigen in pregnancy sera (abstr). *Arthritis Rheum* 1984;27:S20.

13. Deng JS, Sontheimer RD, Giliam JN. Molecular characteristics of SS-B/La and SS-A/Ro cellular antigens. *J Invest Dermatol* 1985;84:86–90.

14. Kephart DC, Hood AF, Provost TT. Neonatal lupus erythematosus: new serologic findings. *J Invest Dermatol* 1981;77:331–333.

15. Taylor PV, Scott JS, Gerlis LM, Esscher E, Scott O. Maternal antibodies against fetal cardiac antigens in congenital complete heart block. *N Engl J Med* 1986;315:667–672.

16. Ishibashi-Ueda H, Yutani C, Imakita M, Kanzaki T, Utsu M, Chiba Y. An autopsy case of congenital complete heart block in a newly born of a mother with systemic lupus erythematosus. *Pediatr Cardiol* 1988;9:157–161.

17. Lee LA, Coulter S, Emer S, Chu H. Cardiac immunoglobulin deposition in congenital heart block associated with maternal anti-Ro autoantibodies. *Am J Med* 1987;83:793–796.

18. Olson NY, Lindsley CB. Neonatal lupus syndrome. *Am J Dis Child* 1987;141:908–910.

19. Litsey SE, Noonan JA, O'Connor WN, Cottrill CM, Mitchell B. Maternal connective tissue disease and congenital heart block. Demonstration of immunoglobulin in cardiac tissue. *N Engl J Med* 1985;312:98–100.

20. Alexander EL, Buyon JP, Lane J, Lafond-Walker A, Provost TT, Guarnier T. Anti-SSA/Ro SSB/La antibodies bind to neonatal rabbit cardiac cells and preferentially inhibit in vitro cardiac repolarization. *J Autoimmun* 1989;2:463–469.

21. Buyon JP, Ben-Chetrit E, Karp S, Roubey RAS, Pompeno L, Reeves WH, Tan EM, Winchester R. Acquired congenital heart block. Pattern of maternal antibody response to biochemically defined antigens of the SSA/Ro-SSB/La system in neonatal lupus. *J Clin Invest* 1989;84:627–634.

Effect of Exercise Training on Left Ventricular Performance in Older Women Free of Cardiopulmonary Disease

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Endurance exercise training increases aerobic exercise capacity (maximal oxygen consumption rate [$\dot{V}O_2$max]) and attenuates the age-related decline in left ventricular (LV) function during exercise in older men. To determine whether similar adaptations occur in older women, 10 subjects (aged 63 ± 4 years mean ± SE) were studied before and after 9 to 12 months of endurance exercise training. They exercised 3.85 ± 0.06 days/week at 81 ± 0.3% of maximal heart rate. LV function at rest and during supine exercise was assessed by radionuclide ventriculography. $\dot{V}O_2$max was increased by 21% (from 1.40 ± 0.1 to 1.7 ± 0.1 liter/min; $p < 0.001$) in response to training. Maximal heart rate and systolic blood pressure during treadmill exercise were unchanged (161 ± 5 beats/min before vs 164 ± 3 beats/min after; p = NS, and 208 ± 7 mm Hg before vs 214 ± 8 mm Hg after; p = NS, respectively) after training. LV ejection fraction at rest (70.4 ± 2% before vs 70 ± 1% after) and during peak exercise (78.6 ± 2% before vs 79.3 ± 2% after) did not change in response to training. Furthermore, the increases in ejection fraction from rest to exercise were similar before and after training (change: 8.8 ± 1 vs 9.1 ± 1%). Stroke volume and cardiac output at peak exercise also did not change in response to training. Exercise training did not induce LV enlargement as evidenced by absence of an increase in LV end-diastolic volume (rest: 117 ± 6 vs 108 ± 9 ml, p = NS; exercise 124 ± 7 ml before vs 123 ± 9 ml after; p = NS). End-systolic volume (rest: 33 ± 2 ml before vs 33 ± 2 ml after, p = NS; exercise: 28 ± 3 ml before vs 25 ± 2 ml after, p = NS), and systolic blood pressure–end systolic volume relation did not change. The results indicate that endurance exercise training improves $\dot{V}O_2$max in older women primarily by means of peripheral adaptations without inducing LV enlargement or enhancement of LV systolic function.

(Am J Cardiol 1993;71:99–104)

The age-related deterioration in cardiovascular function is attributed to structural and functional changes in heart and blood vessels leading to impairment of left ventricular (LV) diastolic function and filling, increased afterload and blunted inotropic and chronotropic responses to catecholamines.[1–6] These changes contribute to the decline in aerobic exercise capacity (maximal oxygen consumption [$\dot{V}O_2$max]) and impaired cardiac performance at maximal exercise often observed in the elderly.[7–10] Primary aging, decreased physical activity, increased adiposity and the presence of asymptomatic coronary disease have been implicated in the decrease in $\dot{V}O_2$max with advancing age. Data from previous studies suggest that $\dot{V}O_2$max declines progressively with age both in men and in women.[10–12] Endurance exercise training induces adaptations that run counter to the age-related decrease in $\dot{V}O_2$ max.[13–15] In older men, the increase in $\dot{V}O_2$max in response to training is in part mediated by development of physiologic LV hypertrophy and improvement in LV function.[14] Although endurance exercise training increases $\dot{V}O_2$ max in older women,[15] no information is available regarding the effects of training on LV function. Therefore, the present study examines whether endurance exercise training enhances LV performance in older women.

METHODS

Subjects: Sixteen sedentary postmenopausal women who were not taking estrogen replacement and met the following criteria were selected from a total of 20 women screened: (1) age 60 to 70 years; (2) absence of symptoms, history of cardiopulmonary disease, or major risk factors for coronary artery disease (3) normal cardiac examination and 12-lead electrocardiogram; and (4) absence of electrocardiographic changes typical of myocardial ischemia during exercise. Six subjects withdrew; 2 because for lack of motivation, 2 because of a change in residence, and 2 because of orthopedic problems. The data on the remaining 10 women, aged 63 ± 4 years (mean ± SE), who completed the study are re-

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ported. All participants gave written informed consent and the study was approved by the Human Studies Committee of Washington University School of Medicine.

Exercise testing and determination of maximal oxygen consumption rate: Each subject initially underwent a standard graded treadmill test as a screening procedure. A repeat treadmill test was performed for determination of $\dot{V}O_2$max within 1 to 2 weeks as previously described in detail.[15] Briefly, during a 5-minute warm-up period, the subjects walked at 1.7 to 2.5 mph on the level to elicit a heart rate response equivalent to 60 to 70% of maximal heart rate.[15] From this point on, the treadmill grade was increased by 2% every 2 minutes until exhaustion. The subjects breathed through a Daniel's valve and the expired gases were measured continually with the use of a computerized system consisting of electronic oxygen (Applied Electrochemistry S3-A) and carbon dioxide (Beckman LB-2) analyzers.[14,15] Inspired air volume was measured with a Parkinson-Cowan dry gas meter calibrated against a Tissot spirometer. $\dot{V}O_2$max was defined as the attainment of a plateau of oxygen uptake with increasing exercise intensities or a respiratory exchange ratio >1.10, or both. In addition, each subject underwent a steady-state (15-minute) submaximal treadmill exercise test requiring approximately 70% of their initial $\dot{V}O_2$max to examine heart rate and blood pressure responses to training at a given absolute intensity.

Left ventricular systolic function: LV function at rest and during supine exercise was assessed using standard electrocardiographic-gated blood pool imaging as previously described.[14] Briefly, after modified in vivo labeling of erythrocytes with stannous pyrophosphate and 25 mCi of technetium-99m, images were obtained with the patients supine using a scintillation camera equipped with a low-energy, high-sensitivity, parallel-hole collimator. The scintillation camera was positioned in the orientation giving best separation, typically 35° to 45° left anterior oblique projection. Modest (15°) caudal angulation was used to give optimal separation of the left atrium and ventricle. Data were collected in frame mode (32 frames per cardiac cycle) in a 64 x 64 pixel matrix and processed off-line with a minicomputer (VAX 11/750). LV ejection fraction was calculated with the use of a count-based technique developed in our laboratory[16] that uses manually defined end-diastolic and end-systolic regions of interest: (ejection fraction = EDC-ESC x 100/EDC), where EDC and ESC are end-diastolic and end-systolic counts, respectively, corrected for backround activity. LV end-diastolic volume was calculated with the use of the standard geometric area-length method of Sandler and Dodge[17]: $V - 8A2/3\ \pi\ l$, where V is volume, A is the area, and l is the long axis of the LV image. Spatial calibration factors for the correction of digital images were obtained using the phantom technique.[18] LV end-systolic volume and stroke volume were derived from LV fractional shortening and LV end-diastolic volume.[14] Cardiac output was calculated as the product of stroke volume and heart rate. After images had been obtained at rest, each subject performed a graded supine exercise test using a cycle ergometer (Engineering Dynamics Corp.) with the initial work rate set at 25 to 50 W followed by 25 W increments every 3 minutes. Images were obtained in the last 2 minutes of each exercise stage in the left anterior oblique projections. Heart rate and blood pressure were measured every minute concurrently with the second minute of data collection. Blood pressure was measured using a standard sphygmomanometer. Peak oxygen uptake was determined in 7 of the subjects during supine cycle ergometer exercise by collecting expired gases in meteorologic balloons which were analyzed by a mass spectrometer (Perkin-Elmer MA 1100) as previously described.[14] LV ejection fraction and end-diastolic volume were measured in a blinded fashion. The reproducibility of LV ejection fraction and LV end-diastolic volume has been reported previously.[14,19]

Body composition: Percent body fat was calculated from body density measured by hydrodensitometry.[20]

Training program: The training program has been described in detail.[14,15] Briefly, each subject completed a 2- to 3-month program of flexibility and stretching exercises to detect and correct any musculoskeletal problem and to select the most suitable mode of training in order to prevent orthopedic problems during the training program. All subjects were advised to avoid performing endurance exercise during this stage. This was verified by a repeat determination of $\dot{V}O_2$max upon completion of the flexibility program. Subjects then began endurance exercises for 9 to 12 months that included walking, running, cycle ergometer and treadmill exercises. They were expected to exercise 5 days/week for 1 hour/session. The initial intensity of exercise was adjusted to require 60 to 70% of the subject's $\dot{V}O_2$max, which gradually increased to 70 to 80% of $\dot{V}O_2$max. $\dot{V}O_2$max was determined every 3 months to monitor the subjects training status and to maintain a constant training intensity relative to the $\dot{V}O_2$max as previously described.[14,15]

Statistics: The differences between data obtained before and after training were evaluated with the use of paired Student's *t* test. Least-squares linear regression was used where appropriate. Data presented are mean ± SE. Differences were considered significant at $p < 0.05$.

RESULTS

Maximal oxygen consumption rate: There was a significant increase in $\dot{V}O_2$max in response to endurance exercise training. During the endurance training phase of the program, subjects exercised an average of 3.85 ± 0.06 days and averaged 11.5 ± 0.32 miles of walk-jog or continuous jogging exercises per week. In addition, they exercised on a cycle ergometer for brief periods. The total caloric expenditure averaged 1,246 ± 33 Kcal/week during the last 4 weeks of the training program. The exercise intensity averaged 81 ± 0.3% of maximal heart rate and was as high as 89 ± 6% of $\dot{V}O_2$max for brief intervals in the final 4 weeks of training program.

$\dot{V}O_2$max at the completion of the flexibility program did not change from the initial value. $\dot{V}O_2$max was increased by 21% (from 1.40 ± 0.07 to 1.7 ± 0.07 liter/min; $p < 0.001$) in response to endurance exercise training.

The respiratory exchange ratio was 1.24 ± 0.05 before and 1.23 ± 0.03 after training (p = NS). Maximal heart rate during treadmill exercise was 161 ± 5 beats/min before and 164 ± 3 beats/min after training (p = NS). Systolic blood pressure at maximal exercise did not change in response to training (208 ± 7 mm Hg before and 214 ± 8 mm Hg after; p = NS). Peak supine cycle ergometer work rate during blood pool imaging was 89 ± 3 W before and 104 ± 3 W after training ($p < 0.001$). Peak oxygen uptake during supine cycle ergometer exercise was increased by 18% ($p < 0.05$) from 1.08 ± 0.06 liter/min (17.7 ± 1.5 ml/kg/min) to 1.27 ± 0.06 liter/min (20.1 ± 1.3 ml/kg/min) in response to training in the 7 women in whom it could be measured. Heart rate at peak supine cycle ergometer exercise was 137 ± 7 and 143 ± 6 beats/min, attaining 85 and 87% of maximal heart rate before and after training, respectively. Heart rate at rest was reduced in the trained state (67 ± 3 vs 62 ± 3 beats/min; $p < 0.025$).

Adaptative responses during submaximal exercise: Exercise training resulted in a significant reduction in heart rate (14%) from 139 ± 9 to 119 ± 5 beats/min ($p < 0.005$), and rate pressure product from $21 \pm 2 \times 10^3$ to $17.7 \pm 2 \times 10^3$ ($p < 0.025$) during a steady-state submaximal exercise test at a constant exercise intensity.

Body composition: There was a significant weight loss from 66.5 ± 3 to 63.3 ± 2 kg ($p < 0.01$) in response to training. Percent body fat was decreased by 8% from 39 ± 2 to 36 ± 2% ($p < 0.01$) after training.

Effects of exercise training on cardiac performance: LV ejection fraction at rest was 70 ± 2% before and 70 ± 1% after training (p = NS). There were similar increases in ejection fraction and mean blood pressure during exercise before and after training, with no differences in either ejection fraction or mean blood pressure at peak exercise between the untrained and trained states (ejection fraction: 79 ± 2% before and 79 ± 2% after [Figures 1 and 2]). LV exercise reserve, defined as ejection fraction change = exercise-rest, was 8.8 ± 1% before and 9 ± 1% after completion of the training program (p = NS; Figure 3). Exercise training resulted in no significant changes in either LV end-diastolic volume or end-systolic volume at rest or peak exercise (Table I). In addition, systolic blood pressure–end systolic volume relation (Figure 4) was unaltered by training. Stroke volume and cardiac output in the entire group did not change either at rest or at peak exercise (Table I, Figure 5). There was a good correlation between cardiac output and work rate both in the untrained and trained states; however, the slopes of the relations

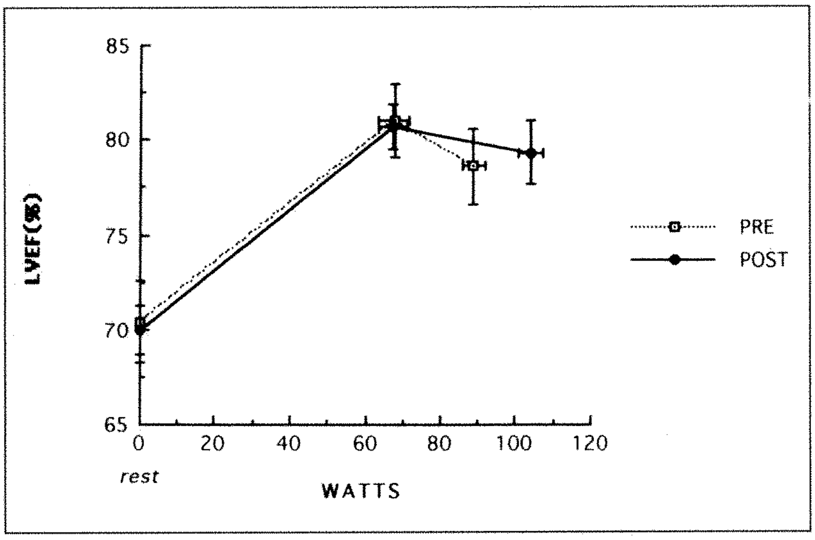

FIGURE 1. Effect of training on left ventricular ejection fraction (LVEF) responses at rest, and during submaximal and peak exercise. Left ventricular ejection fraction peaked at submaximal exercise and did not change at higher work rates both before and after training, with no significant differences between the trained and untrained states.

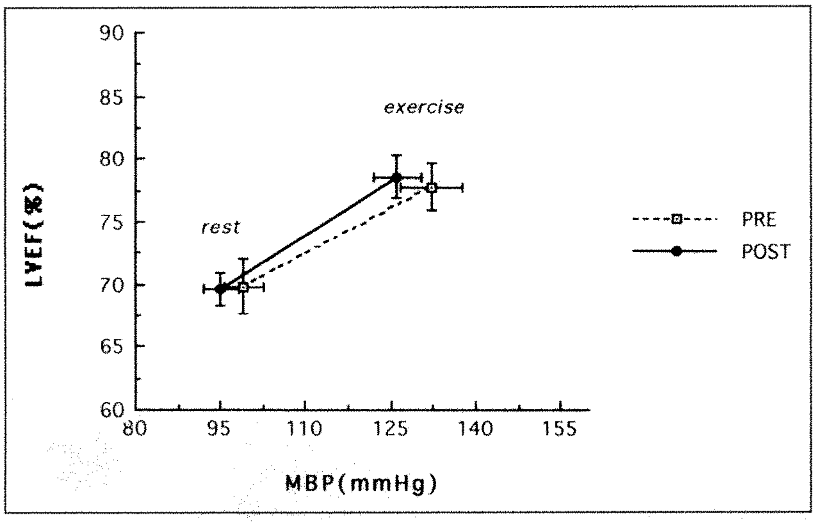

FIGURE 2. Left ventricular ejection fraction (LVEF) responses to training. LVEF values are plotted as a function of mean blood pressure (MBP) used as an estimate of afterload. No differences in LVEF were found at rest or during peak exercise. Mean blood pressure values were similar before and after training (n = 9; mean blood pressure was not available in 1 subject).

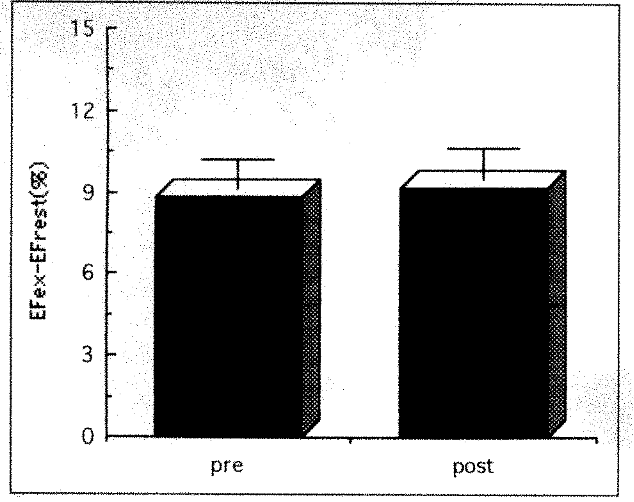

FIGURE 3. Effect of exercise training on left ventricular (LV) exercise reserve, defined as the difference between LV ejection fraction at rest (EFrest) and ejection fraction during peak exercise (EFex), showing no significant training effect.

were similar before and after training (Figure 6). Peak exercise cardiac output in the 7 subjects in whom oxygen uptake was measured simultaneously was 13.5 ± 0.8 liter/min before and 14.5 ± 1 liter/min after training (p = NS). Calculated arteriovenous oxygen content difference at peak supine exercise was increased by 13%, from 8 ± 0.6 to 9 ± 0.8 ml/dl ($p < 0.05$) in these 7 subjects in response to training. Total peripheral resistance decreased significantly during exercise both before (from 1,549 ± 18 to 761 ± 114 dynes s cm^{-5}; $p < 0.01$) and after (from 1,725 ± 144 to 776 ± 73 dynes s cm^{-5} training; $p < 0.01$). However, training did not affect the decline in total peripheral resistance from rest to peak exercise (change from –696 ± 109 before vs –947 ± 136 dynes s cm^{-5} after). LV ejection fraction, stroke volume and cardiac output during submaximal exercise at a given absolute work rate (67 ± 4 W) did not change in response to training.

DISCUSSION

The results of this study indicate that endurance exercise training can increase $\dot{V}O_2max$ in older women to an extent similar to that seen in older men[14,15] without a significant improvement in LV function or the training-induced LV enlargement. Unlike the case with older men,[14] the increase in $\dot{V}O_2max$ in older women in response to training appears to be mediated predominantly by peripheral adaptations as evidenced by widening of arteriovenous oxygen content difference, lower submaximal heart rate and lack of significant increases in cardiac output at peak exercise. The small and insignificant increase in peak exercise cardiac output was entirely due to an increase in heart rate because stroke volume did not change after training. Absence of changes in LV end-diastolic volume, exercise reserve, ejection fraction, and systolic blood pressure–end systolic volume relation in response to training provides further evidence that, in contrast to older men,[14] exercise training does not induce cardiac adaptations in older women. It appears that lack of central adaptations to training is limited only to older women because younger women exhibit LV hypertrophy and enhanced maximal cardiac output in response to training.[21] Within this context, the absence of central adaptations in older women may be, in part, a consequence of estrogen deficiency.

TABLE I Selected Adaptive Responses to Endurance Exercise Training in Older Women

	Before Training	After Training
LV ejection fraction (%)		
Rest	70.4 ± 2	70 ± 1
Exercise	78.6 ± 2	79.3 ± 2
LV end-diastolic volume (ml)		
Rest	117 ± 6	108 ± 9
Exercise	124 ± 7	123 ± 9
LV end-systolic volume (ml)		
Rest	33 ± 2	33 ± 3
Exercise	28 ± 3	25 ± 2
LV stroke volume (ml)		
Rest	84 ± 6	76 ± 6
Exercise	96 ± 6	98 ± 8
Cardiac output (liters/min)		
Rest	5.9 ± 0.5	4.6 ± 0.3
Exercise	12.8 ± 0.7	13.8 ± 0.9
Systolic blood pressure (mm Hg)		
Rest	137 ± 6	130 ± 5
Exercise	197 ± 8	200 ± 9

Values are mean ± SE.

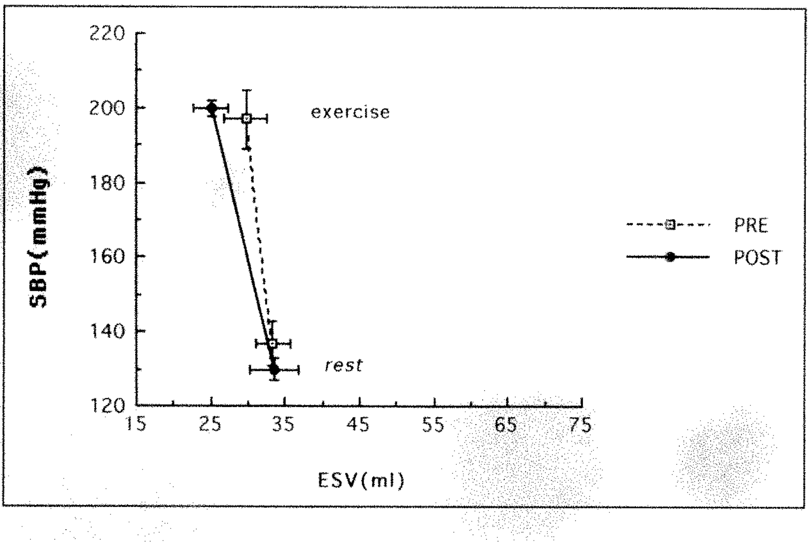

FIGURE 4. Effect of exercise training on left ventricular contractile function assessed with the systolic blood pressure (SBP)–end systolic volume (ESV) relation. No changes in either systolic blood pressure or end-systolic volume at rest or at peak exercise was detected in response training.

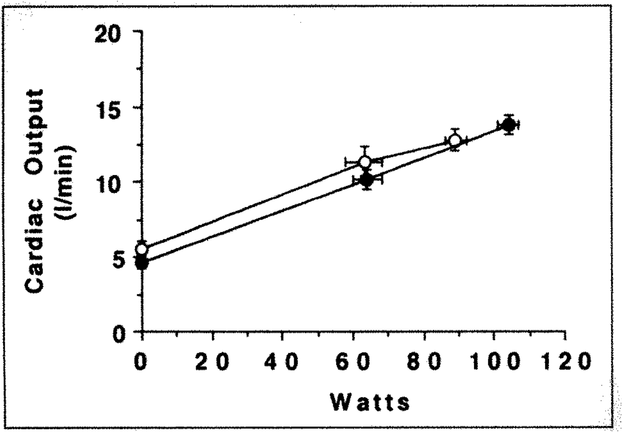

FIGURE 5. Cardiac output at rest, during submaximal exercise at an absolute work rate (67 ± 4 W before vs 67 ± 4 W after), and peak exercise. Training did not have an effect on cardiac output at rest or during supine cycle ergometer exercise. *Open circles*, before; *filled circles*, after.

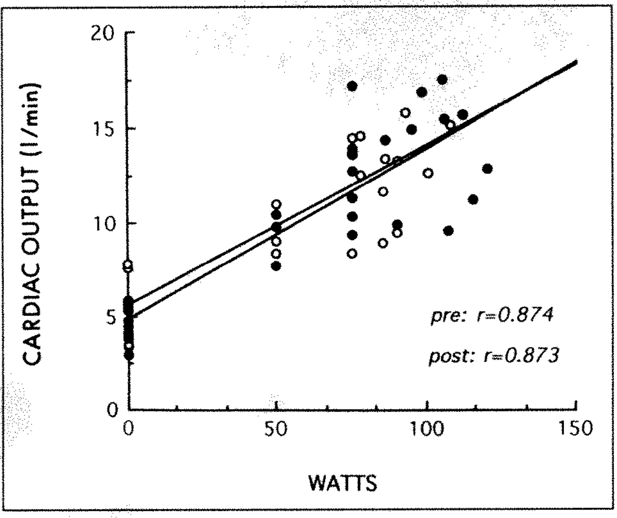

FIGURE 6. The correlation between cardiac output and work rate. The slope of the lines between cardiac output and work rate for the untrained and trained states are similar. *Open circles*, before; *closed circles*, after.

The reasons underlying the disparate adaptive responses to exercise training between older women and men are not clear. A higher LV wall stress at peak exercise, which may have prevented the increase in ejection fraction in the trained state,[22] is unlikely because of lack of increases in blood pressure and total peripheral resistance at peak exercise. Furthermore, similar blood pressure responses during peak exercise between older men[14] and women suggest that possible gender-related differences in afterload may not be large enough to account for differences in adaptations between older men and women. The training intensity relative to $\dot{V}O_2$max and maximal heart rate was similar to that in our study in older men.[14] In absolute terms, however, older men were exercising more intensely[14] than older women in this study. Therefore, it may be that the training intensity in absolute terms may play a role in inducing central adaptations. Another explanation for the gender-related differences in adaptations to training is that, unlike older men, ejection fraction response to exercise in older women can be considered normal because LV exercise reserve averaged 9% before the start of training, which is higher than the values we observed for older men[14] and those reported by others for an elderly population comprising mostly men.[23,24] Therefore, it appears likely that the age-associated deterioration in cardiac performance in women, at least in terms of ejection fraction responses, is modest and much less striking than that observed in men and, as a consequence, the central adaptations to training may also be less conspicuous. The absence of the training-induced LV enlargement, which may be responsible for the lack of central adaptations in older women reflects gender differences or an inadequate training stimulus in absolute terms, or both.

We have recently reported the high reproducibility of ejection fraction and end-diastolic volume at rest and exercise.[14,19] Because radionuclide studies were performed during supine exercise, it is difficult to assess the relative contribution of central and peripheral adaptations to the increase in $\dot{V}O_2$max. Although the number of subjects in our study was small, the lack of cardiac adaptations in this study is not likely to be the consequence of an inadequate sample size, because we have shown central adaptations to training in a comparable number of older men and young women.[14,21] Inclusion of a control group would have been useful. However, it is known that $\dot{V}O_2$max does not improve spontaneously in healthy subjects.[15,25] In addition, we have recently reported the adaptative increase in maximal cardiac output in young women in response to endurance exercise training.[21]

The findings of the present study suggest that endurance exercise training enhances $\dot{V}O_2$max to the same relative magnitude in older women and older men. However, the improvement in $\dot{V}O_2$max in older women is achieved by a different mechanism than that observed in older men.[14] The women did not exhibit LV enlargement or improvement in LV systolic performance to account for the increase in $\dot{V}O_2$max in response to endurance exercise training.

REFERENCES

1. Lakatta, EG, Yin FCP. Myocardial aging: functional alterations and related cellular mechanisms. *Am J Physiol* 1982;242:H927–H941.

2. Lakatta EG, Gerstenblith G, Angell CS, Shock NW, Weisfeldt ML. Diminished inotropic response of aged myocardium to catecholamines. *Circ Res* 1975; 36:262–269.

3. Wei JY, Spurgeon HA, Lakatta EG. Excitation-contraction in rat myocardium: alterations with adult aging. *Am J Physiol* 1984;246:H784–H791.

4. Lakatta EG, Gerstenblith G, Angell CS, Shock NW, Weisfeldt ML. Prolonged contraction duration in aged myocardium. *J Clin Invest* 1975;55:61–68.

5. Yin FCP, Spurgeon HA, Green HL, Lakatta EG, Weisfeldt ML. Age-associated decrease in heart rate response to isoproterenol in dogs. *Mech Ageing Dev* 1979;10:17–25.

6. Yin FCP, Weisfeldt ML, Milnor WR. Role of aortic impedance in the decreased cardiovascular response to exercise with aging in dogs. *J Clin Invest* 1981;68:28–38.

7. Higginbotham MB, Moris KG, Williams RS, Coleman E, Cobb FR. Physiologic basis for the age-related decline in aerobic work capacity. *Am J Cardiol* 1986; 57:1374–1379.

8. Robinson S. Experimental studies of physical fitness in relation to age. *Arbeitphysiologie* 1938;10:251–323.

9. Raven PB, Mitchell JH. The effect of aging on cardiovascular response to dynamic and isometric exercise. In: Weisfeldt ML, ed. The Aging Heart. vol. 12. Aging. New York: Raven Press, 1980:296.

10. Buskirk ER, Hodgson JL. Age and aerobic power: The rate of change in men and women. *Fed Proc* 1987;46:1824–1829.

11. Heath GW, Hagberg JM, Ehsani AA, Holloszy JO. A physiological comparison of young and older athletes. *J Appl Physiol* 1981;51:634–640.

12. Rogers MA, Hagberg JM, Martin III WH, Ehsani AA, Holloszy JO. Decline in $\dot{V}O_2$max with aging in master athletes and sedentary men. *J Appl Physiol* 1990; 68:2195–2199.

13. Seals DR, Hagberg JM, Hurley BF, Ehsani AA, Holloszy JO. Endurance exercise training in older men and women I. Cardiovascular responses to exercise. *J Appl Physiol* 1984;57:1024–1029.

14. Ehsani AA, Ogawa T, Miller TR, Spina RJ, Jilka SM. Exercise training improves left ventricular systolic function in older men. *Circulation* 1991;83:96–103.

15. Kohrt WM, Malley MT, Coggan AR, Spina RJ, Ogawa T, Ehsani AA, Bourey RE, Martin III WH, Holloszy JO. Effects of gender, age and fitness level on the response of VO_2max to training in 60–71 yr olds. *J Appl Physiol* 1991;71:2004–2011.

16. Biello DR, Rampathkumaran KS, Geltman ED, Briston WA, Scott DJ, Girbac RT. Determination of left ventricular ejection fraction: a new method that requires minimal operator training. *J Nucl Med Technol* 1981;9:77–79.

17. Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *Am Heart J* 1968;75:325–334.

18. Seldin DW, Esser PD, Nichols AB, Ratner SJ, Anderson PO. Left ventricular volume determined from scintigraphy and digital angiography by a semiautomated geometric method. *Radiology* 1983;14:809–813.

19. Ehsani AA, Biello DR, Schultz J, Sobel BE, Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 1986;74:350–358.

20. Kohrt WM, Malley MT, Dalsky GP, Holloszy. Body composition of healthy sedentary and trained young and older men and women. *Med Sci Sports Exerc* 1992;24:832–837.

21. Spina RJ, Ogawa T, Martin III WH, Coggan AR, Holloszy JO, Ehsani AA. Exercise training prevents decline in stroke volume during exercise in young healthy subjects. *J Appl Physiol* 1992;72:2458–2462.

22. Ross Jr J. Afterload mismatch and preload reserve: a conceptual framework for analysis of ventricular function. *Prog Cardiovasc Dis* 1976;18:255–264.

23. Rodeheffer RJ, Gerstenblith G, Becker LC, Fleg JL, Weisfeldt ML, Lakatta EG. Exercise cardiac output is maintained with advancing age in healthy human subjects: cardiac dilation and increased stroke volume compensate for a diminished heart rate. *Circulation* 1984;69:203–213.

24. Port S, Cobb FR, Coleman E, Jones RH. Effect of age on the response of the left ventricular ejection fraction to exercise. *N Engl J Med* 1980;303:1133–1137.

25. Hagberg JM. Effect of training on the decline of VO_2max with aging. *Fed Proc* 1987;46:1830–1833.

METHODS

Measurement of Cardiac Output by Automated Single-Breath Technique, and Comparison with Thermodilution and Fick Methods in Patients with Cardiac Disease

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Donald Mahon, MD, and Archie F. Wilson, MD, PhD

Accurate noninvasive methods are needed for determination of cardiac output. Current methods are generally complex or may be unreliable. A previously described method, based on absorption of acetylene gas during a constant exhalation that enables calculation of cardiac output by estimating pulmonary capillary circulation, is incorporated in a new, automated commercial product (SensorMedics 2200). In this study, cardiac output by single-breath acetylene blood flow measured with this device was compared with the standard thermodilution and direct Fick methods in 20 patients undergoing cardiac or pulmonary artery catheterization. Patients inhaled test gas mixture to total lung capacity and exhaled at a constant rate through an adjustable resistor. Lung volumes and noninvasive acetylene blood flow value were calculated automatically. Correlation between the automated single-breath technique and both thermodilution and Fick cardiac output determinations was very high (correlation coefficients were 0.90 and 0.92, respectively), regression slopes were close to identity (0.98 and 0.90), and bias (–0.39 and –0.79 liter/min) and precision (0.94 and 1.02) were good; when shunt correction was applied, bias was reduced to 0.06 and 0.35 liter/min, respectively. Rapid, accurate, noninvasive measurement of cardiac output was easily obtained using the automated device. This technique may have a wide applicability for noninvasive evaluation of patients with cardiac disease and for monitoring effects of therapeutic interventions.

(Am J Cardiol 1993;71:105–109)

Simple, accurate, noninvasive methods for measuring cardiac output are needed. Currently available methods for noninvasive estimation of cardiac output are frequently inconvenient, complex or unreliable. Acetylene gas uptake from alveoli is proportional to pulmonary capillary blood flow and has been extensively demonstrated to accurately estimate cardiac output noninvasively in patients with preserved pulmonary function.[1–5] In this study, we present noninvasive, cardiac output data obtained using a new, automated device that is simple, rapid, and convenient. This approach is based on measurement of acetylene blood flow during 1 slow, constant exhalation using a previously described, clinically validated, mathematical model.[6] Measurements are obtained using a mobile, integrated system. We compared automated, single-breath, noninvasive, acetylene blood flow measurements with pulmonary artery catheter thermodilution cardiac outputs and standard direct Fick measurements.

METHODS

Patients: We studied 20 patients (mean age 43 years, range 17 to 75), 15 undergoing elective cardiac catheterization and 5 who had indwelling pulmonary artery catheters for monitoring. The investigative protocol was approved by the local institutional review board, and signed informed consent was obtained from all patients. Ten patients had valvular heart disease, 3 had coronary artery disease, 3 had cardiomyopathy (2 ischemic and 1 idiopathic), 3 had undergone heart transplantation and 1 had experienced blunt trauma.

Acetylene uptake cardiac output measurement theory: The rate of alveolar absorption of gas that is soluble in tissue and blood (such as acetylene) is proportional to pulmonary capillary blood flow during a single-breath, constant exhalation maneuver.[4,6] A standard factor (height 3.5 g/cm) is applied to account for tissue effect.[7]

Mathematically, the relation between gas absorption and pulmonary capillary blood flow is expressed as follows[6]:

$$\dot{Q}_C = \frac{\ln (F_A/F_{A_0})}{\ln [(V_A + \alpha_t V_t)/(V_{A_0} + \alpha_t V_t)]} * \frac{\dot{V}_E}{\alpha_b} * \frac{60*1,000}{760}$$

where F = fraction of gas; V = volume of gas; $\dot{V}$ = flow rate; α = bunsen coefficient for solubility of acetylene in tissue (t) or blood (b); A = alveolar; A_0 = at full inspi-

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ration; IF = inspiratory flow; I = inspiratory; E = expiratory; and DS = dead space.

During constant flow exhalation, alveolar (as reflected by expired) concentrations of acetylene and carbon monoxide decrease exponentially (Figure 1A). The test gas mixture comprises 0.3% methane, 0.3% acetylene, 0.3% carbon monoxide, 21% oxygen, and balance nitrogen.

Automated single-breath device: The SensorMedics 2200 (Yorba Linda, California) is a pulmonary function test cart that integrates pneumatic, electronic, computer and analyzer components of a pulmonary function test system into a portable unit. The device configuration used in this study includes a mass flow sensor (accuracy ± 3%; 0.1 liter/s) that measures inspiratory and expiratory flows directly, a breath-by-breath nitrogen analyzer (accuracy ± 2%, resolution 0.1% and range 0 to 95% nitrogen), and a rapid-response, multigas, nondispersive, infrared analyzer (accuracy ± 0.006%, resolution 0.0005% and range 0.00 to 0.33%) measuring carbon monoxide, methane and acetylene.

Single-breath procedure: Patients were connected to the mouthpiece of the SensorMedics 2200 machine. A nose clip was used. Patients inhaled to total lung capacity. This was followed by breath-holding of approximately 2 seconds to enable acetylene tissue absorption and gas distribution equilibration. Patients then passively exhaled most of the vital capacity at a constant flow rate of 200 to 500 ml/s (facilitated by positioning an adjustable resistor at the expiratory port).

Two or more trials of automated acetylene blood flow measurement were performed ≥10 minutes apart to ensure residual acetylene washout from blood and tissues. Acetylene blood flow was measured within 15 to 20 minutes of the Fick and thermodilution cardiac output determinations.

Acetylene blood flow: Acetylene blood flow was determined using Equation 1 by obtaining the slope of $\ln(F_A/F_{Ao})$ vs $\ln[(V_A + \alpha_t V_t)/(V_{Ao} + \alpha_t V_t)]$ in the linear region of the constant exhalation phase between dead space washout and closing volume (Figure 1, A and B). Marks delineating the linear phase were positioned automatically at 20 and 80% of exhaled vital capacity. Manual marker adjustments were made to linear portions of the exhalation curves by 2 independent observers unaware of the Fick and thermodilution blood flow measurements.

Thermodilution cardiac output: All patients had pulmonary artery catheters in place. Thermodilution cardiac output measurement was determined using standard techniques on a Marquette Cardiac Output computer. Three to 5 trials were performed, requiring a variability of <20%, and averaged. Thermodilution cardiac output measurements were obtained within 15 minutes of acetylene blood flow determinations.

Fick cardiac output: Cardiac output was also calculated by the standard Fick equation:

$$\text{Cardiac output} = \frac{VO_2}{(ArtO_2Sat\text{-}VenO_2Sat)(Hgb)(13.9)}$$

where VO_2 = oxygen consumption; $ArtO_2Sat$ = arterial oxygen saturation; $VenO_2Sat$ = venous oxygen saturation; and Hgb = hemoglobin.

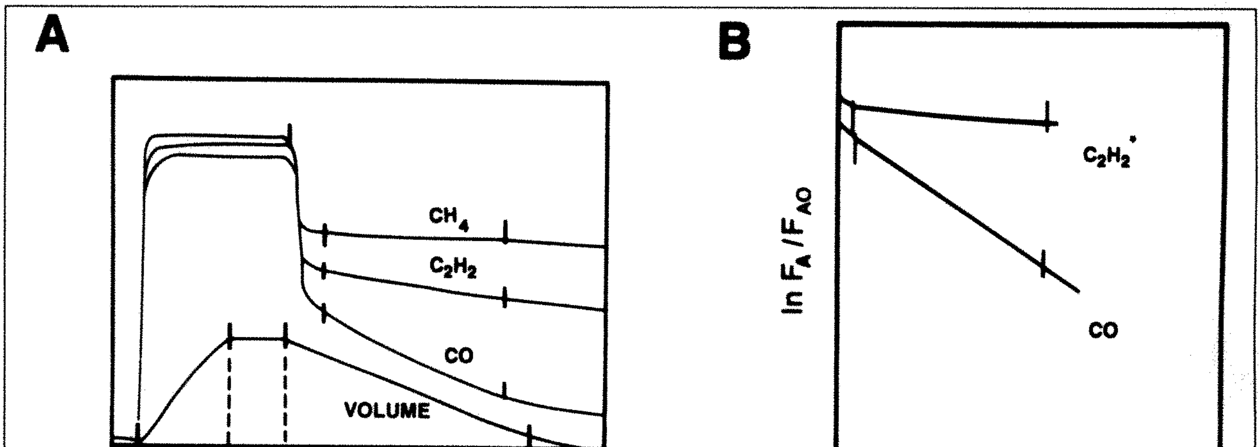

FIGURE 1. *A*, schematic representation of single-breath constant exhalation maneuver gas concentration and volume-time curves used for determination of pulmonary capillary blood flow. Time in seconds is displayed on *abscissa*. Methane (CH_4) concentration used as inert reference gas. Acetylene (C_2H_2) concentration used as absorbable gas. Carbon monoxide (CO) is administered concurrently to measure pulmonary diffusing capacity and is displayed on screen, but is not used in determination of pulmonary capillary blood flow with this device. Volume-time curve for maneuver is displayed with individual inspiratory, breath- holding and expiratory components as labeled. *B*, schematic representation of linear region of log acetylene (corrected for inert gas dilution and initial concentration as $\ln F_A/F_{Ao}$) and natural log alveolar volume relation (corrected for tissue volume as $\ln[(V_A + \alpha_t V_t)/(V_{Ao} + \alpha_t V_t)]$) used in calculating pulmonary capillary blood flow (see Equation 1). *Markers* delineating measurement segment are positioned in linear portion of curve. Again, carbon monoxide curve is displayed for calculation of diffusing capacity, but is not used in pulmonary capillary blood flow determination with this device.

Oxygen consumption was calculated from analyses of exhaled gases. All patients breathed room air. All expired gases were obtained for a measured period of time (3 to 8 minutes were needed to fill the bag) in a 60 liter, nondiffusing bag (#6030, Cal Med, Brea, California). Expired gas was analyzed on a Perkin-Elmer 1100 mass spectrometer (Norwalk, Connecticut). Inspired oxygen values were determined by analysis of room air. The mass spectrometer was calibrated daily before each trial. The volume of exhaled gas was measured on a Tissot Spirometer. All samples were corrected for temperature and humidity. Mixed venous oxygen saturation samples were obtained from the pulmonary artery catheter distal port. Arterial oxygen saturation was determined by aortic blood sampling in patients undergoing cardiac catheterization or by peripheral arterial blood gas in those with an indwelling pulmonary artery catheter. Oxygen saturations were determined on either a Corning model 178 (Medfield, Massachusetts) blood gas machine or an Oxicom 2000 (Waters Inst. Inc.). Hemoglobin was obtained from the Corning model 2500 co-oximeter or from concurrent laboratory complete blood count analysis.

Shunt functions were determined using the Fick cardiac output, arterial and mixed venous oxygen contents with standard formulas[8]: $Qs/Qt = (CiO_2 - CaO_2)/(CiO_2 - C\text{–}\bar{v}O_2)$; where Qs/Qt = shunt fraction; CiO_2 = ideal inspired oxygen content; CaO_2 = arterial oxygen content; and $C\text{–}\bar{v}O_2$ = venous oxygen content.

Statistics: Linear regression was analyzed with the least-squares method (Systat, Inc., Evanston, Illinois). Bias and precision were determined from the mean and standard deviation of the difference between the methods using standard analytical methods.[9–12]

RESULTS

Cardiac output values: Mean acetylene blood flow was 4.77 ± 2.18 liters/min. Mean cardiac outputs for Fick and thermodilution were 5.59 ± 2.13 and 5.16 ± 2.01 liters/min, respectively. When acetylene blood flow was corrected for shunt, average cardiac output was 5.50 ± 2.34 liters/min.

Acetylene blood flow and thermodilution cardiac output correlation: The relation between acetylene blood flow and thermodilution cardiac output is shown in Figure 2A: Slope of regression line was 0.98, correlation 0.9, bias –0.39 liter/min and precision 0.938 liter/min. When acetylene blood flow was corrected for shunt, slope of best fit line was 1.05, correlation 0.9, bias 0.347 liter/min and precision 1.015 liter/min (Figure 2B).

Acetylene blood flow and Fick cardiac output correlation: When acetylene blood flow was compared with Fick cardiac output, slope of regression line was 0.90, correlation coefficient 0.92, bias –0.793 liter/min and precision 0.904 liter/min (Figure 2C). For shunt-corrected acetylene blood flow, correlation coefficient was 0.91, slope 0.97, bias –0.056 liter/min and precision 0.953 liter/min (Figure 2D).

Thermodilution and Fick cardiac output correlation: When Fick and thermodilution cardiac outputs were compared, similar results were obtained; slope of regression line was 0.99, with an r value of 0.98 (Figure 3).

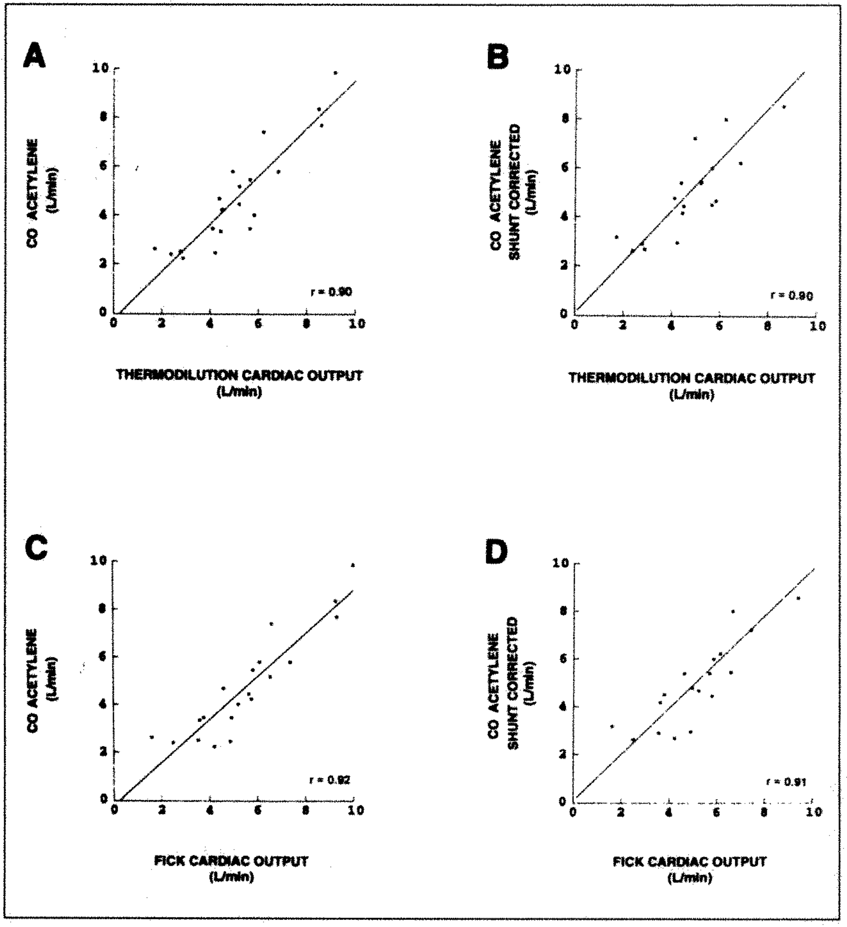

FIGURE 2. Relation between pulmonary capillary blood flow and cardiac output as determined by thermodilution and Fick methods in 20 patients. *A*, correlation between pulmonary capillary blood flow acetylene and thermodilution cardiac output. *B*, correlation between acetylene blood flow and cardiac output by thermodilution after correcting acetylene blood flow by shunt fraction. *C*, correlation between acetylene blood flow and direct Fick cardiac output. *D*, correlation between acetylene blood flow and cardiac output by direct Fick after correcting acetylene blood flow by shunt fraction.

Variability of acetylene blood flow: Mean coefficient of variation between the 2 observers for each acetylene blood flow trial was 6.43%; mean coefficient of variation between acetylene blood flow trials was 13%.

DISCUSSION

There are several methods for clinical measurement of cardiac output. The dye dilution, thermodilution and Fick methods require intravenous lines with attendant complications. Repeat measurements, particularly over extended periods of time, are limited with these invasive methods. Several noninvasive techniques have been developed for estimating cardiac output. Doppler echocardiographic determination of cardiac output has been evaluated in numerous studies.[13] Some problems found with cardiac output measurements by Doppler echocardiography include left ventricular asymmetry,[13] inadequate ultrasound windows and operator variability.[14] In approximately 10 to 20% of patients, Doppler echocardiography cannot be performed.[14,15] Radionuclide scanning requires injection of radiolabeled albumin, expensive scintillation monitors and computer equipment. Repeat measurements of cardiac output are impractical and prohibitively expensive with radionuclide scanning.[16] Impedance cardiography has shown considerable variability in assessing cardiac output.[13]

Numerous studies validating acetylene gas uptake have been published, some using rebreathing techniques. Studies of normal subjects show good correlation with cardiac output.[3,5,17] Rebreathing methods require patients to perform rapid, deep breathing maneuvers. Theoretical and technical problems including changes in alveolar volume and cardiac output during rebreathing maneuvers occur with this method, and can produce errors in the measurement of cardiac output. These difficulties have led to the development of the constant exhalation, single-breath maneuver.[4,6]

The constant exhalation technique involves continuous rapid analysis of gases exhaled at a constant rate after 1 full inhalation of a mixture of absorbable and inert gases. Several studies have validated the constant exhalation, single-breath technique. Elkayam et al[2] compared the single-breath, acetylene technique with thermodilution in 20 cardiac patients and found good correlation.[2] Ramage et al[4] compared the single-breath, acetylene technique with cardiac output estimated by radionuclide scanning and found close correlation.

This study determined cardiac output using an automated SensorMedics 2200 pulmonary function machine. This portable device has rapid infrared sensors for tracking acetylene and carbon monoxide uptake and inert gas concentration, in addition to volume analysis and standard pulmonary function testing. Correlation of the acetylene blood flow technique with the thermodilution and Fick cardiac output methods was high; correlation coefficients were >0.9. Bias and precision were also closely correlated. Correlation of the Fick and thermodilution methods with acetylene blood flow was as strong as that between thermodilution and Fick itself in this study. Accuracy of the acetylene blood flow technique with the mobile SensorMedics 2200 cart was also similar to that of prior studies estimating cardiac output using the mass spectrometer for measurement of single-breath, acetylene gas absorption blood flow.[4,18]

The acetylene method slightly underestimates cardiac output compared with the Fick or thermodilution methods in normal subjects. This is because the acetylene blood flow method reflects pulmonary capillary blood flow and does not measure blood flow shunted by physiologic,

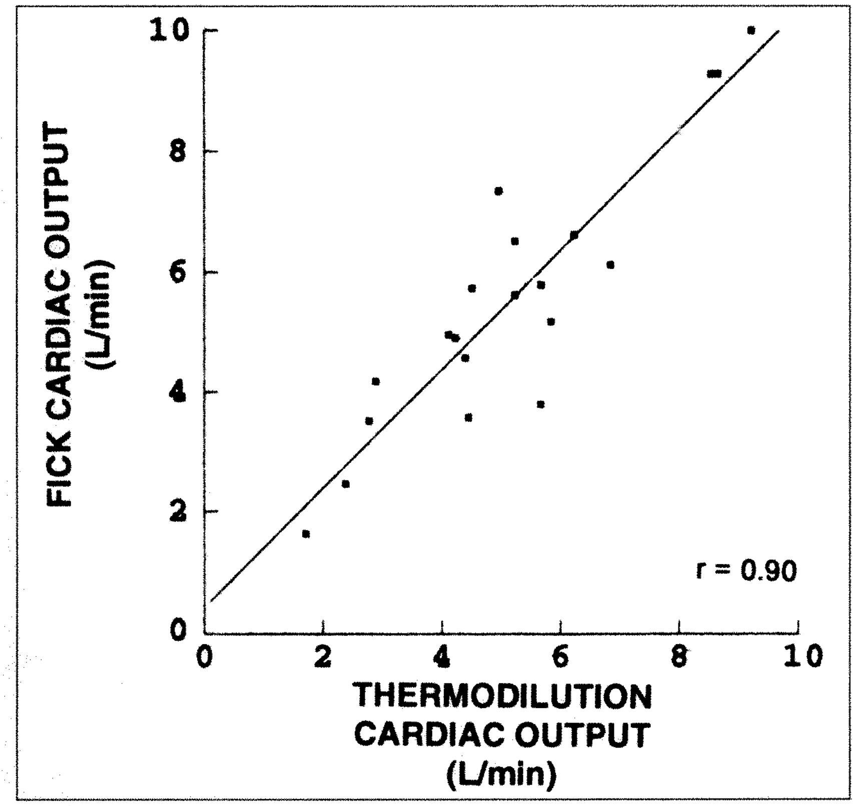

FIGURE 3. Correlation between cardiac output by thermodilution and direct Fick methods.

intracardiac or pulmonary shunts. When physiologic shunt correction was applied to evaluate this effect, all 3 methods showed similar cardiac outputs, and bias was reduced. No patient in this study had significant anatomic shunts. In patients with substantial intracardiac or intrapulmonary shunts, significant underestimation of cardiac output would be expected. In such cases, combining the acetylene blood flow technique with methods for determination of cardiac output not affected by shunting may be helpful in more accurately assessing shunt fractions and evaluating patients with complex shunts.

Whereas the accuracy of acetylene blood flow methods is well-established in patients with preserved lung function,[1–5] it is not known in those with obstructive lung disease, but may be inaccurate due to ventilation-perfusion inhomogeneity. One study suggests that the acetylene blood flow technique may be inaccurate in patients with an $FEV_1/FVC < 60\%$,[2] although Pierce et al[19] found a good correlation when they evaluated 8 patients with ob-structive lung disease.

The accuracy of some maneuvers was limited by the ability of patients to passively exhale at a constant flow rate. This potential problem may be overcome by the placement of a variable resistor designed to cause exhalation that lasts from 4 to 8 seconds. However, Valsalva maneuvers and increased intrathoracic pressures during exhalation should be avoided because of effects on cardiac output and gas concentration measurements. Another potential problem found with this device is the inability to measure residual acetylene concentrations in the lungs before performing maneuvers to verify adequate acetylene washout from the preceding maneuver.

This study confirms the accuracy of an automated, cardiac output measurement method based on well-established principles of acetylene absorption by pulmonary blood flow in patients undergoing cardiac catheterization compared with those of the thermodilution and Fick methods. Incorporation of this method in an automated device has made the technique rapid and easy to perform. In the future, this technology should enable repeated, noninvasive, clinical measurements of cardiac output with attendant clinical and research applications in patients with normal and near normal lung function.

REFERENCES

1. Cander L, Forster R. Determination of pulmonary parenchymal tissue volume and pulmonary capillary blood flow in man. *J Appl Physiol* 1959;14:541–551.

2. Elkayam U, Wilson A, Morrison J, Meltzer P, Davis J, Klosterman P, Louvier J, Henry WL. Non-invasive measurement of cardiac output by a single breath constant expiratory technique. *Thorax* 1984;39:107–113.

3. Sackner M, Greeneltch D, Heiman M, Epstein S, Atkins N. Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume, and cardiac output measured by a rebreathing technique. *Am Rev Respir Dis* 1975;3:157–165.

4. Ramage J, Coleman E, MacIntyre N. Rest and exercise cardiac output and diffusing capacity assessed by a single slow exhalation of methane, acetylene, and carbon monoxide. *Chest* 1987;92:44–50.

5. Triebwasser J, Johnson R, Burpo R, Campbell J, Reardon W, Blomqvist G. Noninvasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. *Aviat Space Environ Med* 1977;48:203–209.

6. Martonen T, Wilson A. Theoretical basis of single breath gas absorption tests. *J Math Biol* 1982;14:203–220.

7. Glauser FL, Wilson AF. Pulmonary parenchymal tissue volume (Vt) in normal subject: the effect of age and sex. *Chest* 1977;72:207–212.

8. West JB. Respiratory Physiology—the Essentials. Baltimore: Waverly Press, 1977:153.

9. Altman D. Statistics and ethics in medical research. *Br Med J* 1980;281:1473–1475.

10. Barker S, Hyatt J. Continuous measurement of intraarterial pHa, $PaCO_2$, and PaO_2 in the operating room. *Anesth Analg* 1991;73:43–48.

11. Bland M, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;2:307–310.

12. DerSimonian R, Charette J, McPeek B, Mosteller F. Reporting methods in clinical trials. *N Engl J Med* 1982;306:1332–1337.

13. Franciosa J. Application of noninvasive techniques for measuring cardiac output in hypertensive patients. *Am Heart J* 1988;116:650–656.

14. Dobb G, Donovan K. Non-invasive methods of measuring cardiac output. *Intensive Care Med* 1987;13:304–309.

15. Dubin J, Wallerson D, Cody R, Devereux R. Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determination. *Am Heart J* 1990;120:116–123.

16. Melin J, Wijns W, Robert A, Nannan M, De Coster P, Beckers C, Detry J-M. Validation of radionuclide cardiac output measurements during exercise. *J Nucl Med* 1985;26:1386–1393.

17. Smyth R, Gledhill N, Froese A, Jamnik V. Validation of noninvasive maximal cardiac output measurement. *Med Sci Sports Exerc* 1984;16:512–515.

18. Morrison J, Wilson A, Vaziri N, Brunsting L, Davis J. Determination of pulmonary tissue volume, pulmonary capillary blood flow and diffusing capacity of the lung before and after hemodialysis. *Int J Artif Organs* 1980;3:259–262.

19. Pierce R, McDonald C, Thuys C, Rochford P, Barter C. Measurement of effective pulmonary blood flow by soluble gas uptake in patients with chronic airflow obstruction. *Thorax* 1987;42:604–614.

No Adaptation to Digitalization as Evaluated by Digitalis Receptor (Na,K-ATPase) Quantification in Explanted Hearts from Donors Without Heart Disease and from Digitalized Recipients with End-Stage Heart Failure

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Speculations about development of tolerance to the inotropic effect of digitalis have been engendered since studies in various in vitro systems and tissues not representative of the heart have shown up-regulation of sodium potassium adenosine triphosphatase (Na,K-ATPase) when exposed to digitalis. Moreover the digitalis receptor (i.e., Na,K- ATPase) concentration in the normal, vital human left ventricle has not been previously determined. On this basis, digitalis receptor concentration was quantified in the left ventricle of explanted hearts from subjects without heart disease and from patients with end-stage heart failure who had received digitalis therapy. This was performed using vanadate-facilitated ^{3}H-ouabain binding to intact tissue samples giving values of 728 ± 58 (n = 5) and 467 ± 55 pmol/g wet weight (n = 6) (mean ± SEM) ($p < 0.005$), respectively. However, some of the digitalis receptors may have retained digoxin before ^{3}H-ouabain binding and thus may have escaped detection. To eliminate this effect of retained digoxin, samples were exposed to prolonged washing in buffer containing excess digoxin antibody, a method recently shown to clear digoxin from receptors and allow subsequent complete digitalis receptor quantification by ^{3}H-ouabain binding. After washing in digoxin specific antibody, specific digitalis receptor concentration was 760 ± 58 pmol/g (n = 5) and 614 ± 47 pmol/g (n = 6) wet weight in samples of the normal and failing hearts, respectively ($p < 0.08$). Thus, digitalization was associated with occupancy of digitalis receptors in the failing human heart of 24% ($p < 0.02$). After washing with antibody, the digitalis receptor concentration tended to be lower (19%) in the failing than in the normal hearts. Thus, there was no evidence for development of adaptation to digitalization due to up-regulation of the digitalis receptor concentration when comparing the failing and healthy human heart.

(Am J Cardiol 1992;70:110–114)

The myocardial sodium potassium adenosine triphosphatase (Na,K-ATPase) is generally accepted to be the receptor for digitalis and mediator of its inotropic action.[1] It is unknown whether in patients with heart failure treated with digoxin the abundance of the digitalis receptor in the left ventricle is up-regulated, leading to tolerance to the inotropic effect of the drug. The digitalis receptor concentration can be determined with high accuracy and precision in intact human myocardial samples using vanadate-facilitated ^{3}H-ouabain binding.[2] Measurements have hitherto been carried out on myocardial tissue obtained postmortem,[2,3] or on endomyocardial biopsies obtained during cardiac catheterization.[4,5] One problem with studies of ^{3}H-ouabain binding to myocardial tissue from patients who have had digitalis therapy has been that some of the receptors were occupied by digoxin before ^{3}H-ouabain binding.[4,5] However, prolonged washing of samples in buffer containing excess digoxin antibody fragments has recently been found to reduce prior specific digoxin binding in the human left ventricle by approximately 95%, and subsequently allows complete quantification of digitalis receptors by vanadate-facilitated ^{3}H-ouabain binding.[6] With this approach accurate studies of digitalis receptor concentration in myocardium from digitalized patients have become possible.

Previous studies on the development of tolerance to digitalis in various in vitro systems and tissues not representative of the heart have shown upregulation of Na, K-ATPase when exposed to digitalis[7–15] and studies on humans have been inconclusive.[16–19] Against this background, the first aim of the present study was to determine the digitalis receptor concentration in normal human myocardium without confounding effects of postmortem degradation of receptors. This was done by measuring digitalis receptor concentration in explanted

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human hearts from subjects without heart disease. Second, our aim was to solve the persisting question of whether digitalis treatment induces up-regulation of Na,K-ATPase concentration in the human heart with end-stage heart failure. This was feasible by comparing ^{3}H-ouabain binding to intact samples of human myocardium from subjects without heart disease with that from patients given digoxin with end-stage heart failure after prolonged washing of samples in buffer with digoxin antibody.

METHODS

Materials: Myocardial tissue was obtained from 11 adults entering the transplantation program as organ donors or heart recipients at Brigham and Women's Hospital, Boston, Massachusetts. The study was conducted in accordance with a protocol approved by the Committee for the Protection of Human Subjects at Brigham and Women's Hospital in accordance with the Helsinki Declaration II. Five subjects (4 men and 1 women, aged 21 to 34 years [mean 28]) were organ donors due to brain death, and 6 male subjects (aged 32 to 50 years [mean 45]) were heart recipients because of end-stage heart failure. Information was obtained from the medical records about (1) severity of heart failure according to the New York Heart Association classification, (2) ejection fraction determined by ventriculography, (3) digoxin treatment (daily dosage, duration of treatment, serum digoxin level), and (4) serum potassium. Specimens of the left ventricle were obtained from all subjects. Hearts from brain dead subjects were harvested 1 to 10 days (mean 2) after institution of life support. The only cardioactive drug administered during this period was dopamine. None of these patients had received digoxin. Immediately after kidney harvest, the hearts were removed, the coronary arteries were examined for atheroma, and samples of the free wall of the left ventricular myocardium were emerged in liquid nitrogen within 5 minutes after heart explantation and stored at –70°C. The hearts from the patients with end-stage heart failure were obtained during heart transplantation. In all cases the etiology of heart failure was ischemic heart disease. All the heart recipients were receiving therapy for angina pectoris and heart failure including digoxin treatment. Serum digoxin was measured by radioimmunoassay as previously described in detail.[20] Within 5 minutes after explantation, specimens of the left ventricular free wall, sampled from areas without macroscopic fibrosis, were submerged in liquid nitrogen and stored at –70°C.

^{3}H-ouabain binding: All procedures were performed using a freshly made vanadate buffer containing 10 mmol/liter of tris(hydroxymethyl)aminomethane (TRIS) chloride, 250 mmol/liter of sucrose, 3 mmol/liter of magnesium sulfate and 1 mmol/liter of vanadate. The pH was adjusted to 7.3 with TRIS chloride.

Clearance of digoxin from its specific receptor was performed by washing samples in buffer containing excess specific digoxin Fab as previously described in detail.[6] In brief, 5 to 6 samples in the wet weight range of 4 to 8 mg were cut from the original specimens and placed in 12 ml buffer containing specific digoxin Fab at a concentration of 5×10^{-7} mol/liter at 30°C for 16 hours. This has been found to reduce prior digoxin binding in the human left ventricle by about 95% and to allow subsequent vanadate-facilitated complete quantification of ^{3}H-ouabain binding sites.

The digitalis receptors were quantified using standard ^{3}H-ouabain binding as previously described in detail.[2] In brief, samples were prewashed for 20 minutes (2 times 10 minutes) at 0°C in buffer to thaw and preincubate with vanadate and also to reduce extracellular specific digoxin Fab in experiments performed after washing of samples in digoxin antibody. To determine total uptake and retention of ^{3}H-ouabain, incubations took place in buffer containing ^{3}H-ouabain (2.1 μCi/ml) and ouabain added to a final concentration of 1×10^{-6} mol/liter for 2 hours (2 times 1 hour) at 37°C. After incubations a washout at 0°C in unlabeled buffer for 2 hours (4 times 30 minutes) was performed to reduce the amount of ^{3}H-ouabain in the extracellular space, thereby enhancing the precision of the method. Nonspecific uptake and retention of ^{3}H-ouabain was determined by incubating samples at similar conditions except in a surplus of unlabeled ouabain (i.e., at a ^{3}H- ouabain (2.1 μCi/ml) and ouabain concentration of 1×10^{-3} mol/liter). After washout samples were blotted, weighed and soaked overnight in vials containing 0.5 ml of 5% w/v trichloroacetic acid. Thereafter, 2.5 ml scintillation mixture (Opti-fluor®) was added, and the ^{3}H- activity in samples and incubation medium assayed by liquid scintillation counting. On the basis of sample wet weight, the ^{3}H-activity in the incubation medium and the ^{3}H-activity retained in the samples, the ^{3}H-activity taken up was calculated and expressed as the relative uptake (i.e., ^{3}H-activity taken up per gram wet weight of tissue relative to the ^{3}H-activity in 1 ml incubation medium and given as a decimal fraction). To determine the specific uptake and retention of ^{3}H-ouabain, the value obtained for nonspecific uptake and retention was subtracted from the total uptake and retention. The concentration of ^{3}H-activity in the samples was then expressed in pmol/g wet weight by multiplying the relative uptake of ^{3}H-activity with the concentration of ouabain in the incubation medium.

Chemicals and isotopes: All chemicals were of analytic grade. Specific digoxin antibody (ovine), Digibind®, was from the Wellcome Foundation Ltd. (Kent, United Kingdom), ouabain from Sigma (St. Louis, Missouri), vanadate from Merck (Darmstad, Germany), ^{3}H-ouabain (22.1 Ci/mmol) from Amersham International (Buckinghamshire, United Kingdom), and Opti-fluor® from Packard Instruments (Downers Grove, Illinois). The purity of the ^{3}H-ouabain was checked by the Na,K-ATPase extraction method as the percentage of ^{3}H-activity that could bind to purified Na,K-ATPase.[21]

Statistics: Results are given as mean ± SEM, with the number of observations in parentheses. Statistical significance of differences was ascertained by using Student's 2-tailed *t* test for paired observations within the groups of organ donors and patients with end-stage heart failure, and by using Student's 2-tailed *t* test for unpaired observations between the 2 groups, respectively.

TABLE I Clinical Details of Subjects Studied

	Treated with Digoxin	Not Treated with Digoxin
No. of subjects	6	5
Men:women	6:0	4:1
Mean age (year)	45 ± 5	28 ± 2
Duration of digoxin treatment	22 months (3 weeks–5 years)	—
Serum potassium (mmol/liter)	4.2 ± 0.1	4.3 ± 0.1
NYHA	III–IV	—
Ejection fraction (%)	20 (11–29)	> 55
Cardiologic diagnosis	Coronary artery disease	Normal
Cause of death	—	Brain death

Values are mean ± SEM with ranges in parentheses.
NYHA = New York Heart Association.

The minimal sample size was calculated: A total of 10 subjects were necessary to show a statistically significant difference of ≥190 pmol/g wet weight between the 2 groups, accepting a type 1 error of 5% and a type 2 error of 20% with SD measurements of 110 pmol/g wet weight.

RESULTS

The clinical details of the enrolled subjects are given in Table I. Patients with end-stage heart failure had been treated with digoxin ranging from 3 weeks to 5½ years (mean 22 months) before heart transplantation. In the group with heart failure, serum digoxin concentration was within the therapeutic range (0.9 to 1.8 ng/ml) in all cases. All subjects had serum potassium levels within the normal range (3.5 to 5.0 mmol/liter). New York Heart Association class was III to IV among the digoxin-treated subjects. Ejection fraction was between 11 and 29% (mean 20).

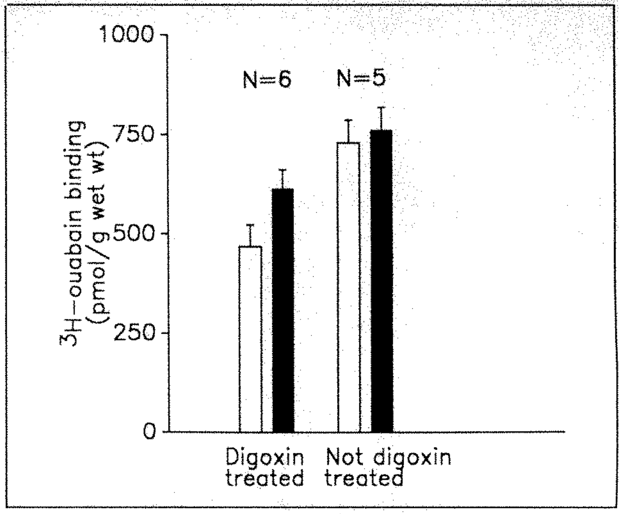

FIGURE 1. Mean values for ^{3}H-ouabain binding before and after clearance of previously bound digoxin in samples of the left ventricle from 6 patients (heart recipients) treated with digoxin and from 5 control subjects (potential organ donors) not exposed to digoxin. ^{3}H-ouabain binding was determined using vanadate-facilitated ^{3}H-ouabain binding to intact myocardial specimens *(open columns)*. Clearance of previously bound digoxin was performed by washing samples in buffer containing excess fragments of digoxin antibody and was followed by vanadate-facilitated ^{3}H-ouabain binding *(closed columns)*. *Bars* denote SEM.

Standard ^{3}H-ouabain binding measurements of left ventricular samples from digoxin-treated patients with heart failure was 467 ± 55 (n = 6), and from those without heart disease unexposed to digoxin, it was 728 ± 58 (n = 5) pmol/g wet weight (Figure 1). There was no variation in nonspecific ^{3}H-ouabain binding between groups or as a result of procedures (p >0.10). Thus, ^{3}H-ouabain binding was 36% lower in those who received

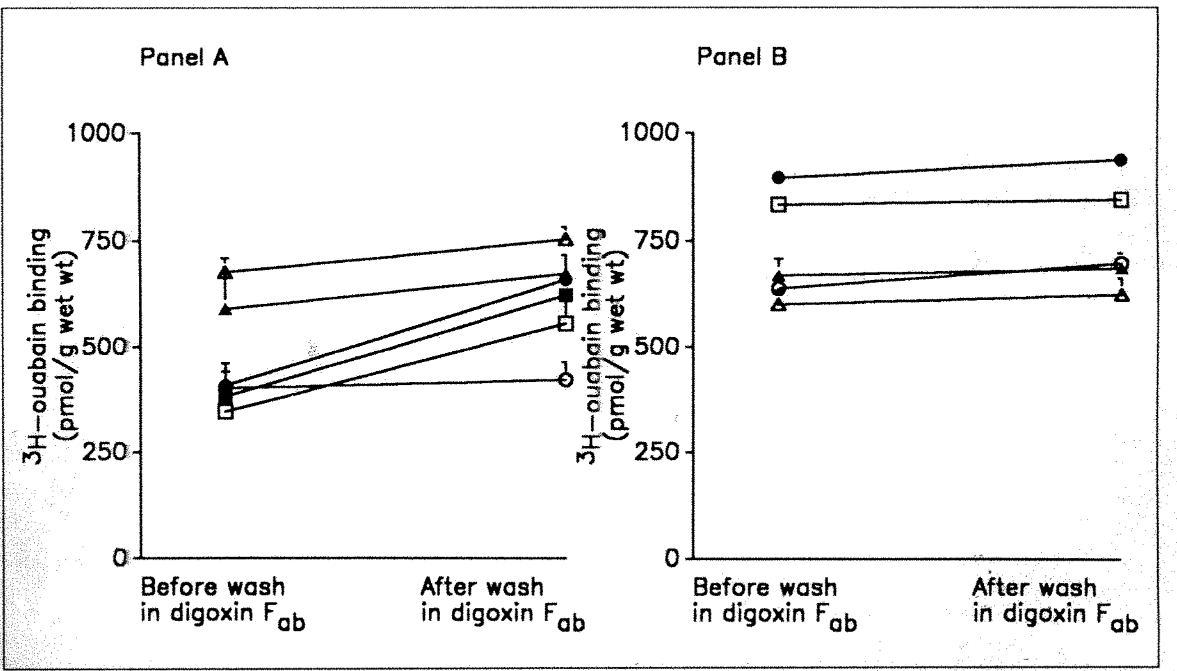

FIGURE 2. Individual values for ^{3}H-ouabain binding to left ventricles described in Figure 1. *Panels A and B* show ^{3}H-ouabain binding before and after washing in digoxin-specific antibody fragments in the recipient and potential donor groups, respectively. Each *point* represents the mean value for observations on 6 samples from 1 patient. *T bars* denote SEM where these exceed the size of the *symbols*. Values from each subject are connected. F_{ab} = fragment antigen-binding.

versus those who did not receive digitalis ($p < 0.005$). After prolonged washing in digoxin antibody, ^{3}H-ouabain binding measurements were 614 ± 47 ($n = 6$) and 760 ± 58 pmol/g wet weight ($n = 5$), respectively ($p < 0.08$) (Figure 1). Thus, ^{3}H-ouabain binding was now only 19% lower in samples from those who received versus those who did not receive digitalis therapy.

Figure 2 gives the individual values for ^{3}H-ouabain binding after washing previously bound digoxin off the cardiac glycoside receptors in left ventricular samples from the digoxin-treated group (Figure 2, panel A), and exposing samples from the untreated group to the same procedure (Figure 2, panel B). All patients with heart failure had an increase in ^{3}H-ouabain binding after clearance of previously bound digoxin. The increase in ^{3}H-ouabain binding was more pronounced in all but 1 of the patients with heart failure than in samples from subjects without heart disease. None of the values obtained in the patients with heart failure after clearance of previously bound digoxin reached the mean level for ^{3}H-ouabain binding in samples from the control group exposed to the same procedure.

Because patients with heart failure had received digoxin for periods varying from 3 weeks to 5½ years, it was of interest to evaluate whether duration of treatment might influence the digitalis receptor concentration. Thus, ^{3}H-ouabain binding site concentration determined after clearance of receptors for previously bound digoxin was compared with duration of digoxin treatment. This gave no evidence of a relation between duration of treatment and concentration of receptors.

Within the group of subjects exposed to digoxin there was an increase of 31% ($p < 0.02$) in left ventricular ^{3}H-ouabain binding after clearing receptors of previously bound digoxin. The mean occupancy of receptors with digoxin as a result of digoxin treatment was 24% ($p < 0.05$).

Since the occupancy of receptors with digoxin varied between 5 and 39% among subjects, it was also of interest to evaluate whether occupancy of receptors with digoxin might influence the digitalis receptor concentration. Thus, ^{3}H-ouabain binding after clearance of receptors for previously bound digoxin was compared with occupancy of receptors. This gave no evidence of a relation between occupancy of receptors by digoxin and concentration of receptors.

Within the group of patients unexposed to digoxin, there was a small but significant increase in mean left ventricular ^{3}H-ouabain binding after washing of samples in specific digoxin Fab fragments (4%, $p < 0.05$) (Figures 1 and 2, panel B).

DISCUSSION

The present study for the first time quantifies the total number of Na,K pumps in normal, vital, human left ventricular myocardium (728 ± 58 pmol/g wet weight [$n = 5$]). This value may be compared with previous reports from our group of a ^{3}H-ouabain binding site concentration of 413 ± 26 ($n = 5$) observed in the human left ventricle obtained 6 hours after death from patients with no known heart disease,[2] and of 559 ± 62 pmol/g wet weight ($n = 5$) in left ventricular endomyocardial biopsy specimens taken during cardiac catheterization from patients with suspected idiopathic dilated cardiomyopathy but with normal left ventricular function as determined by ventriculography.[4] Thus, evaluation of the concentration of Na,K pumps in normal, vital left ventricular myocardium gave 1.8- and 1.3-fold higher values than in necropsy samples and endomyocardial biopsy samples, respectively. The lower values in tissue obtained at necropsy may be due to postmortem degradation,[2] and in these samples as well as in endomyocardial biopsy samples, the Na,K-pump concentration may have been reduced because of undiagnosed heart disease.[4,5]

Compared with normal subjects no evidence for up-regulation of myocardial digitalis receptor concentration during digitalization was found in the present study. Furthermore, there was no correlation between Na,K-pump concentration and duration of digitalization or with occupancy of receptors by digoxin. The present observation is in agreement with a previous study on human myocardial tissue obtained at necropsy from patients who have received digitalis therapy.[20] On the other hand, the present study is at variance with studies of cultured cells,[7–13] peripheral blood cells[16–19] and guinea pig myocardium,[14,15] all of which showed up-regulation of Na,K-ATPase as a result of digitalis exposure. However, both cultured cells and peripheral blood cells have previously been shown to have a regulation of Na,K-ATPase different from muscle tissue.[22] Furthermore, studies[14,15] on guinea pig myocardium were performed using measurements of Na,K-ATPase activity in membrane fractions with ensuing potential for recovery problems.[23,24] Thus, the observation of no development of tolerance on the heart receptor level to digoxin treatment supports clinical trials indicating that withdrawal of digoxin treatment from patients with heart failure is associated with clinical deterioration and the inotropic effect of digoxin is maintained during treatment.[25]

The present study indicates an occupancy of digitalis receptors in vivo of around 24% during digitalization. This may be compared with an occupancy of receptors with digoxin of around 34% in human left ventricular samples obtained at necropsy from patients treated with digoxin.[20] This concordance indicates that degradation of Na,K pumps as well as release of digoxin from receptors postmortem may occur with almost equal velocity. Thus, evaluation of occupancy of receptors with digoxin in samples obtained postmortem seems validated. Furthermore, the present study is in agreement with the report of a 38% reduction in maximal hyperpolarization of resting membrane potential in atrial tissue from patients treated with digoxin undergoing heart valve operations.[26] Measurements of digoxin content by radioimmunoassay in myocardial samples have given values of around 78 to 112 ng/g wet weight,[27,28] corresponding to around 100 to 143 pmol/g wet weight. In the present study the occupancy observed corresponds to a digoxin content of around 150 pmol/g wet weight. Thus, these studies appear to be in reasonable agreement and may indicate that a major part of digoxin bound to the heart during digitalization is specifically bound to the Na,K pump.

A trend toward lower Na,K-ATPase concentration in myocardial tissue from patients with heart failure compared with control subjects was observed in the present study. This difference is probably not due to mere chance ($p < 0.08$), although the difference does not reach conventional levels for statistical significance. In previous studies on endomyocardial biopsies of the left ventricle from patients with dilated cardiomyopathy and an ejection fraction <40%, a 36% lower ^{3}H-ouabain binding compared with that in patients with ejection fraction above this value has been found.[4] The decrease in left ventricular ^{3}H-ouabain binding cannot be explained by a mere increase in fibrous tissue content in patients with dilated cardiomyopathy[4] or in those with ischemic heart disease.[20] Furthermore, with ischemic heart disease, a reduction of around 37% in ^{3}H-ouabain binding in human myocardial tissue has been observed.[5] In conclusion, the normal human left ventricular myocardium has been found to have a Na,K-pump concentration of 728 ± 58 pmol/g wet weight, and when compared with the normal heart no evidence was noted to support an adaptation to digitalization because of up-regulation of digitalis receptor concentration in the failing human heart.

Acknowledgment: We thank Grete Simonsen for skilled technical assistance, Stig Haunsø for valuable discussions, and the Wellcome Foundation for a gift of digoxin antibody fragments (Digibind®).

REFERENCES

1. Smith TW. Digitalis: mechanisms of action and clinical use. *N Engl J Med* 1988;318:358–365.

2. Nørgaard A, Kjeldsen K, Hansen O, Clausen T, Larsen CG, Larsen FG. Quantification of the ^{3}H-ouabain binding site concentration in human myocardium: a postmortem study. *Cardiovasc Res* 1986;20:428–435.

3. Kjeldsen K, Grøn P. Age-dependent change in myocardial cardiac glycoside receptor (Na,K-pump) concentration in children. *J Cardiovasc Pharmacol* 1990;15:332–337.

4. Nørgaard A, Bagger JP, Bjerregaard P, Baandrup U, Kjeldsen K, Thomsen PE. Relation of left ventricular function and Na,K-pump concentration in suspected idiopathic dilated cardiomyopathy. *Am J Cardiol* 1988;61:1312–1315.

5. Nørgaard A, Kjeldsen K. Human myocardial Na,K-pumps in relation to heart disease. *J Appl Cardiol* 1989;4:239–245.

6. Schmidt TA, Kjeldsen K. Enhanced clearance of specifically bound digoxin from human myocardial and skeletal muscle samples by specific digoxin antibody fragments. Subsequent complete digitalis glycoside receptor (Na,K-ATPase) quantification. *J Cardiovasc Pharmacol* 1991;17:670–677.

7. Boardman LJ, Lamb JF, McCall D. Uptake of (^{3}H)ouabain and Na pump turnover rates in cells cultured in ouabain. *J Physiol Lond* 1972;225:619–635.

8. Vaughan GL, Cook JS. Regeneration of cation-transport capacity in HeLa cell membranes after specific blockade by ouabain. *Proc Natl Acad Sci U S A* 1972;69:2627–2631.

9. Pollack LR, Tate EH, Cook JS. Na$^+$, K$^+$-ATPase in HeLa cells after prolonged growth in low K$^+$ or ouabain. *J Cell Physiol* 1981;106:85–97.

10. Aiton JF, Lamb JF, Ogden P. Down-regulation of the sodium pump following chronic exposure of HeLa cells and chick embryo heart cells to ouabain. *Br J Pharmacol* 1981;73:333–340.

11. Kim D, Marsh JD, Barry WH, Smith TW. Effects of growth in low potassium medium or ouabain on membrane Na,K-ATPase, cation transport, and contractility in cultured chick heart cells. *Circ Res* 1984;55:39–48.

12. Werdan K, Reithmann C, Erdmann E. Cardiac glycoside tolerance in cultured chicken heart muscle cells — a dose-dependent phenomenon. *Klin Wochenschr* 1985;63:1253–1264.

13. Brodie C, Sampson SR. Effects of chronic ouabain treatment on [^{3}H]ouabain binding sites and electrogenic component of membrane potential in cultured rat myotubes. *Brain Res* 1985;347:121–123.

14. Bluschke V, Bonn R, Greeff K. Increase in the (Na$^+$ + K$^+$)-ATPase activity in heart muscle after chronic treatment with digitoxin or potassium deficient diet. *Eur J Pharmacol* 1976;37:189–191.

15. Bonn R, Greeff K. The effect of chronic administration of digitoxin on the activity of the myocardial (Na + K)-ATPase in guinea-pigs. *Arch Int Pharmacodyn Ther* 1978;233:53–64.

16. Ford AR, Aronson JK, Grahame Smith DG, Carver JG. Changes in cardiac glycoside receptor sites, ^{86}rubidium uptake and intracellular sodium concentrations in the erythrocytes of patients receiving digoxin during the early phases of treatment of cardiac failure in regular rhythm and of atrial fibrillation. *Br J Clin Pharmacol* 1979;8:125–134.

17. Aronson JK, Ford AR, Grahame Smith DG. Techniques for studying the pharmacodynamic effects of cardiac glycosides on patients' own erythrocytes during glycoside therapy. *Klin Wochenschr* 1981;59:1323–1332.

18. Erdmann E, Werdan K, Krawietz W. Influence of digitalis and diuretics on ouabain binding sites on human erythrocytes. *Klin Wochenschr* 1984;62:87–92.

19. Rapeport WG, Aronson JK, Grahame-Smith DG, Carver JG. Increased specific ^{3}H-ouabain binding to lymphocytes after incubation with acetylstrophanthidin for 3 days. *Br J Clin Pharmcol* 1985;20:277P–278P.

20. Schmidt TA, Holm-Nielsen P, Kjeldsen K. No upregulation of digitalis glycoside receptor (Na,K-ATPase) concentration in human heart left ventricle samples obtained at necropsy after long term digitalization. *Cardiovasc Res* 1991;25:684–691.

21. Hansen O, Skou JC. A study on the influence of the concentration of Mg^{2+}, P$_i$, K$^+$, Na$^+$, and Tris on (Mg^{2+} + P$_i$)-supported g-strophanthin binding to (Na$^+$ - K$^+$) activated ATPase from ox brain. *Biochim Biophys Acta* 1973;311:51–66.

22. Kjeldsen K. Regulation of the concentration of ^{3}H-ouabain binding sites in mammalian skeletal muscle — effects of age, K-depletion, thyroid status and hypertension. *Dan Med Bull* 1987;34:15–46.

23. Jones LR, Besch HR. Isolation of canine cardiac sarcolemmal vesicles. *Meth Pharmacol* 1984;5:1–12.

24. Hansen O, Clausen T. Quantitative determination of Na$^+$-K$^+$-ATPase and other sarcolemmal components in muscle cells. *Am J Physiol* 1988;254:C1–C7.

25. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539–544.

26. Rasmussen HH, Okita GT, Hartz RS, Ten Eick RE. Inhibition of electrogenic Na(+)-pumping in isolated atrial tissue from patients treated with digoxin. *J Pharmacol Exp Ther* 1990;252:60–64.

27. Coltart J, Howard M, Chamberlain D. Myocardial and skeletal muscle concentrations of digoxin in patients on long-term therapy. *Br Med J* 1972;2:318–319.

28. Karjalainen J, Ojala K, Reissell P. Tissue concentrations of digoxin in an autopsy material. *Acta Pharmacol Toxicol* 1974;34:385–390.

Prognostic Significance of Silent Myocardial Ischemia in Patients >61 Years of Age with Extracranial Internal or Common Carotid Arterial Disease With and Without Previous Myocardial Infarction

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Patients with extracranial carotid disease (ECD) have an increased incidence of coronary events.[1-3] We are reporting data from a prospective study correlating silent myocardial ischemia detected by 24-hour ambulatory electrocardiography with the incidence of new coronary events at 43-month mean follow-up in elderly patients with 40 to 100% ECD with and without coronary artery disease (CAD).

In a prospective study, technically satisfactory 24-hour ambulatory electrocardiography was performed using portable Avionics tape recorders (model 445) or SpaceLabs 2-channel recorders (model 90205) to obtain 2 leads corresponding to modified leads V_1 and V_5 in 161 patients with 40 to 100% ECD diagnosed by carotid duplex ultrasonography. Bilateral carotid duplex ultrasonography was performed as previously described[4]: V_{max} 0.80 to 1.75 m/s = 40 to 80% arterial luminal diameter reduction; V_{max} >1.75 m/s = 80 to 99% arterial luminal diameter reduction; and V_{max} 0.00 m/s (no Doppler signal on ≥2 separate tests) = 100% arterial luminal diameter reduction.

The tapes were analyzed using a CardioData Mk 3 computer system or a SpaceLabs FT 2000 computer system. ST-segment changes were written out on electrocardiographic paper at a speed of 25 mm/s and interpreted by 2 cardiologists. Patients with marked ST-segment depression (≥1.5 mm) at rest were excluded from the study. Silent ischemia was diagnosed if horizontal or downsloping ST-segment depression ≥1.0 mm below the level at rest occurred at 80 ms after the J point, lasted for ≥1.0 minute and was unassociated with anginal symptoms. If ST-segment depression at rest occurred, an additional 2.0 mm of ischemic ST-segment depression below the level at rest at 80 ms after the J point was needed. Complex ventricular arrhythmias included ventricular tachycardia or paired, multiform or frequent (≥30/hour) ventricular premature complexes.

The 161 patients included 51 men and 10 women, mean age 81 ± 8 years (range 62 to 98). Of 161 patients with ECD, 93 (58%) had CAD. Patients were considered at entry into the study to have CAD if they had a documented clinical history of myocardial infarction, or electrocardiographic evidence of Q-wave myocardial infarction (91 patients), or typical angina pectoris without previous myocardial infarction (2 patients).

Mean follow-up from the day 24-hour ambulatory electrocardiography was performed was 43 ± 20 months (range 3 to 68). New coronary events were diagnosed if the patient developed myocardial infarction, primary ventricular fibrillation or died suddenly. Myocardial infarction was diagnosed as previously described.[5] Sudden cardiac death was defined as an unexpected cardiac death in a patient within 1 hour of being clinically stable.[6] All coronary events and causes of death were reviewed by the senior investigator, with the physician taking care of the patient.

Fisher's exact tests were used to analyze data (Tables I and II). Survival curves for coronary events in patients with CAD, with and without silent ischemia (Figure 1), and for coronary events in those without CAD, with and without silent ischemia (Figure 2), were estimated using the Kaplan-Meier product limit estimator and tested for homogeneity with the log-rank and Wilcoxon tests. The relation between 12 prognostic variables and time to development of coronary events was

TABLE I Correlation of Silent Ischemia with Incidence of New Coronary Events at 43-Month Follow-Up in Elderly Patients with Extracranial Internal or Common Carotid Arterial Disease

	Coronary Events	
	Silent Ischemia	No Silent Ischemia
	No. (%)	No. (%)
ECD with CAD	35/38 (92%)*	37/55 (67%)
ECD without CAD	14/18 (78%)†	15/50 (30%)

*p <0.005; †p <0.001.
ECD = extracranial carotid arterial disease; CAD = coronary artery disease.

TABLE II Correlation of Number of Episodes of Silent Ischemia, Maximal ST-Segment Depression, and Duration of Silent Ischemia with Incidence of New Coronary Events in Elderly Patients with Extracranial Internal or Common Carotid Arterial Disease

	Coronary Events	
	No. (%)	p Value
≥5 episodes/day of SI	13/14 (93%)	NS
1 to 4 episodes/day of SI	36/42 (86%)	
≥2.0 mm of maximal ST-segment depression	29/30 (97%)	<0.05
1.0 to 1.9 mm of maximal ST-segment depression	20/26 (77%)	
≥60 minutes/day of SI	32/34 (94%)	NS
1 to 59 minutes/day of SI	17/22 (77%)	

SI = silent ischemia.

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analyzed using the multivariate Cox regression model (Table III).

Silent ischemia was present in 38 of 93 patients (41%) with ECD and CAD and in 18 of 68 patients (26%) with ECD without CAD. Table I shows the correlation of silent ischemia with new coronary events in patients with ECD and CAD and in patients with ECD without CAD. Table I also lists levels of statistical significance. Table II indicates the correlation of number of episodes of silent ischemia, degree of maximal ST-segment depression, and duration of silent ischemia in elderly patients with ECD with new coronary events.

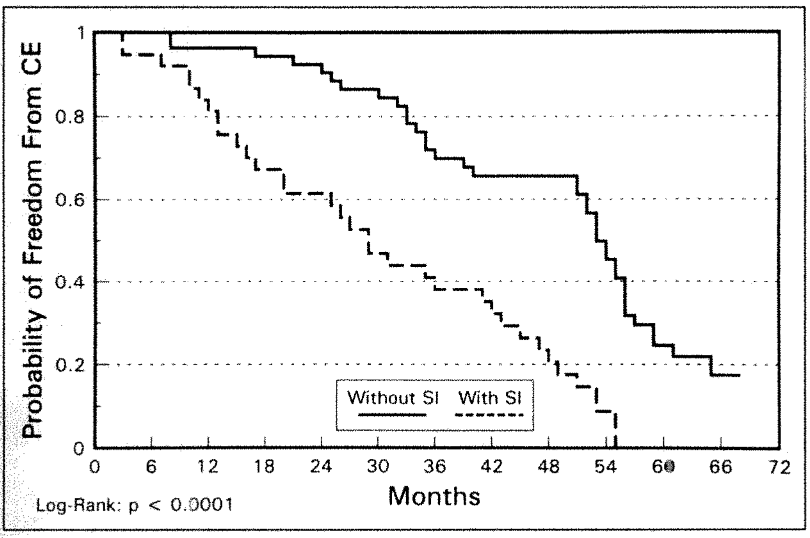

FIGURE 1. Kaplan-Meier survival curves for development of coronary events (CE) in patients with extracranial internal or common carotid arterial disease and coronary artery disease, with and without silent ischemia (SI).

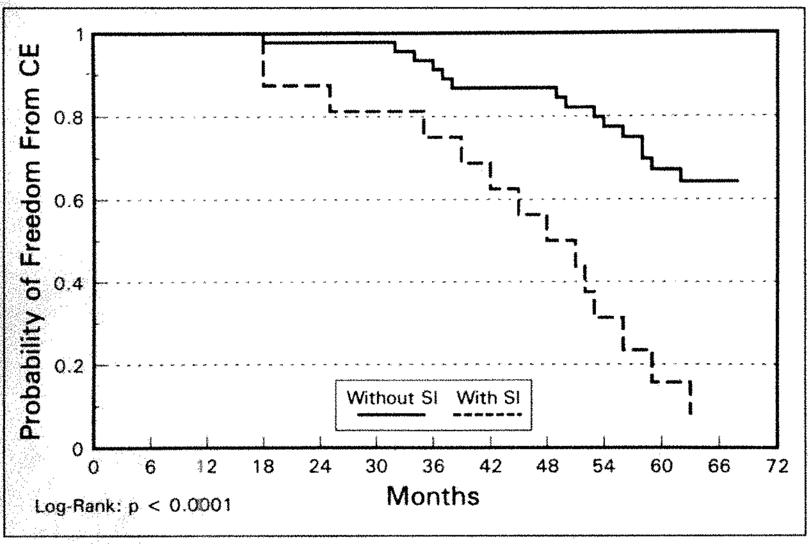

FIGURE 2. Kaplan-Meier survival curves for development of coronary events (CE) in patients with extracranial internal or common carotid arterial disease without coronary artery disease, with and without silent ischemia (SI).

TABLE III Prognostic Variables for Coronary Events and Their Regression Coefficients in the Multivariate Cox Regression Model

Variable	Regression Coefficient	Standard Error	p Value	Relative Risk	95% Confidence Limits
Silent ischemia	1.366	0.237	0.000	3.919	(2.464, 6.232)
Prior CAD	0.820	0.243	0.000	2.271	(1.410, 3.658)
Serum high-density lipoprotein cholesterol (mg/dl)	−0.051	0.015	0.001	0.951	(0.922, 0.980)
Cigarette smoking	0.640	0.251	0.013	1.896	(1.159, 3.101)
Systemic hypertension	0.390	0.228	0.084	1.478	(0.945, 2.310)
Serum total cholesterol (mg/dl)	0.005	0.003	0.111	1.005	(0.999, 1.012)
Serum triglycerides (mg/dl)	−0.002	0.002	0.415	0.998	(0.994, 1.002)
Sex	−0.153	0.250	0.543	0.858	(0.526, 1.401)
Diabetes mellitus	0.125	0.236	0.600	1.133	(0.713, 1.799)
Complex ventricular arrhythmias	0.102	0.246	0.676	1.108	(0.684, 1.793)
Obesity*	0.100	0.455	0.828	1.105	(0.453, 2.693)
Age (year)	0.002	0.014	0.915	1.002	(0.975, 1.029)

*$\geq$20% above ideal body weight.
CAD = coronary artery disease; sex = 0 if men and 1 if women.

Table II also lists levels of statistical significance. The log-rank and Wilcoxon tests show that the 2 survival curves for the development of coronary events are significantly different (p <0.0001) between the patient groups with and without silent ischemia for patients with (Figure 1) and without (Figure 2) CAD, respectively. Table III lists 12 prognostic variables for coronary events and their regression coefficients in the multivariate Cox regression model. There was a 40% decrease in the development of coronary events for an increase of 10 mg/dl in serum high-density lipoprotein cholesterol after controlling other variables.

Patients with unstable angina pectoris,[7,8] at high-risk after infarction,[9] with prior myocardial infarction,[10–12] with stable angina pectoris,[13,14] with peripheral arterial disease,[12,15,16] and elderly patients with systemic hypertension, valvular heart disease, or cardiomyopathy without CAD[11] have an increased incidence of cardiovascular morbidity and mortality. The results from our prospective study of 161 patients with ECD showed that silent myocardial ischemia detected by 24-hour ambulatory electrocardiography was associated with an increased incidence of new coronary events in patients with and without clinical evidence of CAD. In patients with silent ischemia, the incidence of coronary events was increased in those with ≥2.0 mm of maximal ST-segment depression compared with that in patients with 1.0 to 1.9 mm of maximal ST-segment depression. However, the incidence of new coronary events was not significantly different in patients with ≥5 episodes/day of silent ischemia compared with those with <5 episodes/day or in those with ≥60 minutes/day of silent ischemia compared with those with 1 to 59 minutes/day.

This study also showed that silent myocardial ischemia was the most important independent risk factor for new coronary events in our elderly population with ECD. After controlling for other prognostic variables, patients with silent ischemia had a 3.9 times greater chance of developing new coronary events than did those without silent ischemia. Other independent risk factors for new coronary events in this study were prior CAD (relative risk 2.3), serum high-density lipoprotein cholesterol (relative risk 0.95), and cigarette smoking (relative risk 1.9). Whether medical or surgical treatment of silent myocardial ischemia can improve the long-term prognosis of these patients and how much reduction in silent ischemia may be clinically relevant remains to be determined by future studies.

REFERENCES

1. Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. *N Engl J Med* 1986;315:860–865.

2. Ford CS, Frye JL, Toole JF, Lefkowitz D. Asymptomatic carotid bruit and stenosis: a prospective follow-up study. *Arch Neurol* 1986;43:219–222.

3. Aronow WS, Schoenfeld MR. Forty-five-month follow-up of extracranial carotid arterial disease for new coronary events in elderly patients. *Coronary Artery Dis* 1992;3:249–251.

4. Aronow WS, Schoenfeld MR, Paul P. Risk factors for extracranial internal or common carotid arterial disease in persons aged 60 years and older. *Am J Cardiol* 1989;63:881–882.

5. Aronow WS. Prevalence of presenting symptoms of recognized acute myocardial infarction and of unrecognized healed myocardial infarction in elderly patients. *Am J Cardiol* 1987;60:1182.

6. Roberts WC. Sudden cardiac death: definitions and causes. *Am J Cardiol* 1986;57:1410–1413.

7. Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody PV, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* 1987;10:1–9.

8. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. *J Am Coll Cardiol* 1987;10:756–760.

9. Gottlieb SO, Gottlieb SH, Achuff SC, Baumgardner R, Mellits ED, Weisfeldt ML, Gerstenblith G. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. *JAMA* 1988;259:1030–1035.

10. Tzivoni D, Gavish A, Zin D, Gottlieb S, Moriel M, Keren A, Banai S, Stern S. Prognostic significance of ischemic episodes in patients with previous myocardial infarction. *Am J Cardiol* 1988;62:661–664.

11. Aronow WS, Epstein S. Usefulness of silent myocardial ischemia detected by ambulatory electrocardiographic monitoring in predicting new coronary events in elderly patients. *Am J Cardiol* 1988;62:1295–1296.

12. Aronow WS, Ahn C, Mercando A, Epstein S. Prognostic significance of silent ischemia in elderly patients with peripheral arterial disease with and without previous myocardial infarction. *Am J Cardiol* 1992;69:137–139.

13. Rocco MB, Nabel EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 1988;78:877–884.

14. Tzivoni D, Weisz G, Gavish A, Zin D, Keren A, Stern S. Comparison of mortality and myocardial infarction rates in stable angina pectoris with and without ischemic episodes during daily activities. *Am J Cardiol* 1989;63:273–276.

15. Ouyang P, Gerstenblith G, Furman WR, Golueke PJ, Gottlieb SO. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol* 1989;64:1113–1116.

16. Raby KE, Goldman L, Cook EF, Rumerman J, Barry J, Creager MA, Selwyn AP. Long-term prognosis of myocardial ischemia detected by Holter monitoring in peripheral vascular disease. *Am J Cardiol* 1990;66:1309–1313.

Ventricular Fibrillation Markers on Admission to the Hospital for Acute Mcardial Infarction

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Primary ventricular fibrillation (VF) is an early complication of acute myocardial infarction (AMI), which was recently associated with high in-hospital mortality.[1] The usefulness of preventive antiarrhythmic drugs in patients with symptoms of acute coronary ischemia has been addressed in different studies,[2,3] but less attention has been given to the identification of AMI patients with a high risk for VF. Admission data for predicting VF in AMI have been assessed by Flugelman et al[4,5] and Molstad[6] using multiple logistic regression formulas. In the first study, however, ventricular tachycardia was included as the end point for analysis, and no distinction was made between primary and secondary VF, whereas in the second study, only variables of doubtful value in clinical practice were considered. We investigated the usefulness of routine clinical, electrocardiographic and laboratory parameters for predicting

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TABLE I Clinical, Electrocardiographic and Laboratory Data on Admission to the Hospital in 85 Acute Myocardial Infarction Patients With and 187 Without Ventricular Fibrillation (control group)

Variable	VF Group	Control Group	p Value
Age (year)	57 ± 11	57 ± 10	NS
Cigarette smokers	70%	68%	NS
Time from onset of pain and admission (min)	165 ± 162	178 ± 154	NS
SBP (mm Hg)	128 ± 29	147 ± 29	<0.001
Electrocardiogram			
Heart rate (beats/min)	76 ± 24	77 ± 18	NS
ΣST (3 leads)	13 ± 17	8 ± 11	<0.005
Mean QTc (Bazett)	0.41 ± 0.03	0.41 ± 0.03	NS
Inferior site	69%	56%	<0.05
2nd-/3rd-degree AV block	15%	8%	<0.005
Arrhythmias (QRS ≥0.12 second)*	13%	6%	<0.05
Laboratory			
Kalemia (mEq/L)	3.8 ± 0.4	3.9 ± 0.4	NS

*Without hemiblock or bundle branch block.
AV = atrioventricular; SBP = systolic blood pressure; VF = ventricular fibrillation.

the development of VF in patients with AMI in Killip's functional class I and II.

TABLE II Predictive Model of Logistic Regression in Half of Patients Selected at Random

	SBP >110 mm Hg	Inferior Site	ΣST >10 mm (3 leads)	Arrhythmia in the ECG
Coefficient	−0.79	1.22	1.65	0.4241
SE	0.64	0.5	0.47	0.5217
OR	0.4	3.4	5.2	1.5
95% CI of OR				
Lower limit	0.2	2.1	3.2	0.9
Upper limit	0.9	5.6	8.4	2.6

Constant:coefficient = −1.8362. The coefficient of the constant is provided to enable calculation of probability of developing VF.
CI = confidence interval; ECG = electrocardiogram; OR = odds ratio; SBP = systolic blood pressure.

A group of 85 patients (74 men and 1 women, mean age 57 years) with AMI in Killip's class I and II who developed VF within the first 12 hours after admission to the hospital were retrospectively selected from among 1,888 AMI patients admitted to the coronary unit during the past 10 years (208 patients with Killip's class III and IV). The control group comprised 187 patients (169 men and 18 women, mean age 57 years) with AMI in Killip's class I and II without VF who were admitted to the hospital consecutively within 12 hours after the onset of symptoms during 1981 and 1987 (23 patients were excluded because of Killip's class III and IV, and 55 because no electrocardiograms were available within 12 hours after the onset of symptoms of AMI). The diagnosis of AMI was based on the presence of ≥2 of the following findings: typical chest pain, characteristic changes in the 12-lead electrocardiographic recording, and increase in serum creatine kinase or creatine kinase myocardial subfraction. The mean time elapsed from the onset of symptoms to hospital admission was 165 ± 162 minutes in patients with VF and 178 ± 154 minutes in control subjects (p = NS).

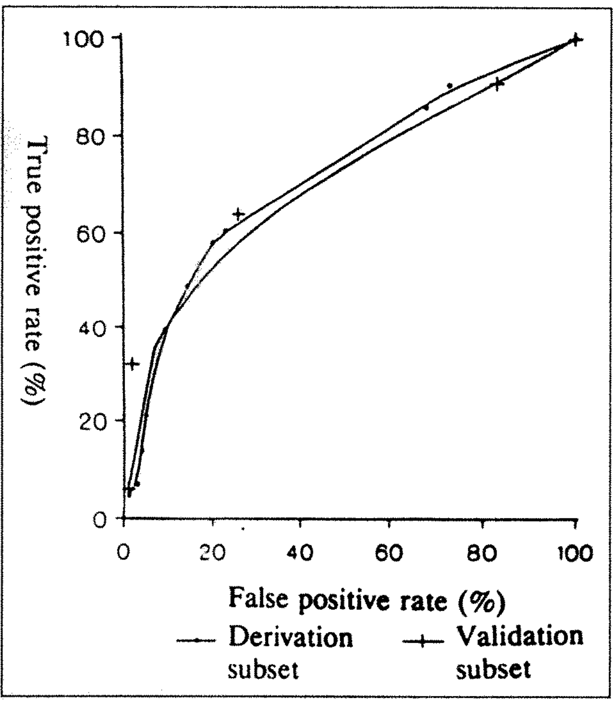

FIGURE 1. Receiver-operating characteristic curves show probability of ventricular fibrillation in derivation and validation subsets calculated by logistic regression model.

A set of clinical, hemodynamic, laboratory and electrocardiographic variables related to occurrence of VF were prospectively assessed on admission. The chi-square test was used for analysis of the relation between pairs of categoric variables, and the Student's t *test for continuous and dichotomous variables. Continuous variables were categorized into dichotomous variables for logistic regression modeling purposes. Cutoff values were established in accordance with clinical criteria. Variables that reached statistical significance (p <0.05) in the bivariate analysis were included in a logistic regression model. A model was fitted with half of patients chosen at random (derivation subset). The predictive power of the model was tested in the remaining patients (validation subset). Receiver-operating characteristic[7] curves were used to assess the proportion of true- and false-positive results generated by different cutoff values in the predicted probability of VF. The areas under the curves for each subset of patients were compared by the method of Hanley and McNeil.[8]*

Bivariate analysis showed that patients in the VF group were significantly different from control subjects in the mean values or proportions of the following variables (Table I): systolic blood pressure >10 mm Hg on admission, inferior localization of necrosis, sum of ST >10 mm in 3 electrocardiographic leads, arrhythmias in the electrocardiogram on admission, second- or third- degree heart block, and QRS >0.12 second in the absence of branch block or hemiblock pattern. Infarction size (as evaluated 4 days after admission by the simplified QRS score)[9] was similar in both groups. In-

hospital mortality was significantly higher in patients with VF (15%) than in control subjects (4%) ($p <0.01$).

When the regression model was fitted with the data from the derivation subset, only systolic blood pressure >10 mm Hg, inferior site of infarction, and ΣST >10 mm in 3 electrocardiographic leads contributed significantly to the predictive capacity of the model (Table II). Systolic blood pressure >10 mm Hg showed a protective effect on the occurrence of VF (odds ratio 0.4, and 95% confidence interval 0.2–0.9), whereas the remaining parameters contributed as risk factors. The predictive capacity of the model did not change significantly when the validation subset was applied (Figure 1). A 60.5% sensitivity and 77% specificity were obtained using a cutoff value of 0.4 in the model-predicted probability. The positive predictive value was 12%, according to the actual prevalence of VF (4.5%) in our hospital. Using a cutoff value of 0.2, the sensitivity of the model increased to 90.3%, but the specificity decreased to 27% and the positive predictive value to 6%.

In this study, simple measurements such as systolic blood pressure >110 mm Hg, inferior infarction, and sum of ST >10 mm in 3 electrocardiographic leads were identified as predictive factors for VF in AMI patients with no congestive heart failure. QTc interval, low diastolic blood pressure and maximal elevation of the ST segment in the electrocardiographic record were previously identified as predictive factors by Flugelman et al.[4,5] In those studies, however, the numbers of patients were small, the time interval between the onset of symptoms and collection of data was not considered, and no distinction was made between congestive heart failure–related VF and primary VF. Blatt et al[10] have shown the protective effect of reactive systemic hypertension in dogs. In the study of Presley et al,[11] a higher mortality was found among AMI patients with normotension and tachycardia than among those with hypertension and tachycardia. The relevance of the degree of ST elevation has not been systematically assessed in patients with AMI, but our results and those of Flugelman et al[4,5] stress the high predictive value of this parameter on admission. In the present study, however, the greater proportion of inferior infarcts could be explained by the exclusion of patients in Killip's functional class III and IV.

In summary, on the basis of simple clinical measurements such as systolic blood pressure >110 mm Hg, inferior infarct location, and sum of ST >10 mm in 3 electrocardiographic leads, 90% of patients with AMI in Killip's class I and II with high risk for VF can be identified on admission. However, a large proportion of these patients will never develop VF, according to the low prevalence of VF among our patients with AMI.

Acknowledgment: We thank Marta Pulido, MD, for editorial assistance.

REFERENCES

1. Volpi A, Moggioni A, Franziosa MG, Pampallona S, Mauri F, Tognoni G. In-hospital prognosis of patients with acute myocardial infarction complicated by primary ventricular fibrillation. *N Engl J Med* 1987;317:257–261.
2. Kostner RW, Dunning PJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. *N Engl J Med* 1985;313:1105–1110.
3. Dubois C, Pierard L, Albert A, Smeets JP, Demoulin JC, Boland J, Kulbertus H. Short-term risk stratification at admission based on simple clinical data in acute myocardial infarction. *Am J Cardiol* 1988;61:216–219.
4. Flugelman MY, Hasin Y, Tur-Caspa I, Friedlander Y, Gostman MS. Prediction of in-hospital ventricular fibrillation from admission data in acute myocardial infarction. *Clin Cardiol* 1983;6:156–162.
5. Flugelman MY, Flugelman AA, Rozeman J, Bed-David J, Shefer A, Koren G, Gostman MS. Prediction of atrial and ventricular fibrillation complicating myocardial infarction from admission data: a prospective study. *Clin Cardiol* 1987; 10:503–505.
6. Molstad P. Primary ventricular fibrillation in acute myocardial infarction. *J Intern Med* 1989;226:107–111.
7. Feinstein AR. Clinical Epidemiology. Philadelphia: W.B. Saunders, 1985:601–609.
8. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–843.
9. Wagner GS, Freye ChJ, Palmeri ST, Roark SF, Staqck NC, Ideker RE, Harrel FE, Selvester RH. Evaluation of a screening system for estimating myocardial infarct size. I. Specificity and observer agreement. *Circulation* 1982;65:342–347.
10. Blatt CHM, Verrier RL, Lown B. Acute blood pressure elevation and ventricular fibrillation threshold during coronary occlusion and reperfusion in dogs. *Am J Cardiol* 1977;39:523–528.
11. Presley JC, Severance HW, Raney MP, McKinnis RA, Smith MW, Hindman MC, Hadley Wilson B, Wagner GS. A comparison of paramedic versus basic emergency medical care of patients at high and low risk during acute myocardial infarction. *J Am Coll Cardiol* 1988;12:1556–1562.

Elevated Circulating Levels of Beta 2-Microglobulin in Patients with Idiopathic Dilated Cardiomyopathy

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Beta 2-microglobulin is a low molecular weight protein of 11.6 kD found on the surface of nearly all nucleated cells.[1] There it constitutes the light invariant chain of the class I major histocompatibility molecule, which is involved in the the antigen presentation during interaction with T lymphocytes.[1] Beta 2-microglobulin appears in free soluble form in serum where it is increased in states of T cell activation, i.e., in viral infections,[2,3] and chronic inflammatory, autoimmune and lymphoproliferative disorders.[4,5] Its serum concentration also depends on renal function because the kidneys are the main site of clearance.[6] The marked retention during chronic renal failure results in the formation of the dialysis-associated amyloid whose major protein is β 2-microglobulin.[7] Samsonov et al[8] recently described β 2-microglobulin as a serologic marker for cellular immune activation in inflammatory heart diseases. We report here that elevated plasma values correlated both with the stimulation of the renin-angiotensin system due to re-

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TABLE I Hemodynamic Findings in 36 Patients with Idiopathic Dilated Cardiomyopathy

Left ventricular ejection fraction*	0.20 ± 0.02
Right ventricular ejection fraction*	0.31 ± 0.03
Right atrial mean pressure (mm Hg)	7.1 ± 0.9
Right ventricular end-diastolic pressure (mm Hg)	6 ± 1
Pulmonary artery mean pressure (mm Hg)	25 ± 2
Pulmonary capillary wedge pressure (mm Hg)	16 ± 2
Cardiac index (liters/min/m^2)	2.7 ± 0.1
Pulmonary vascular resistance (dynes s min^{-5})	168 ± 23
Systemic vascular resistance (dynes s min^{-5})	1404 ± 82

*Right and left ventricular ejection fractions were determined by radionuclide ventriculography in the 30 patients with sinus rhythm; 6 patients with atrial fibrillation were excluded.

duced renal perfusion and with T cellular hyperresponsiveness in patients with idiopathic dilated cardiomyopathy (IDC). Thus, β 2-microglobulin reflects different factors in the complex pathophysiology of IDC.

Thirty-six patients with IDC (30 men and 6 women, aged 52 ± 2 years) were investigated consecutively between December 1989 and November 1990 at the Department of Cardiology, University of Vienna. The positive control group consisted of 19 patients with invasively diagnosed 2- or 3-vessel coronary artery disease who had a comparable degree of concomitant heart failure, i.e., "ischemic cardiomyopathy." Thirty age- and sex- matched healthy donors and 20 patients with coronary artery disease and normal left ventricular function composed the negative control groups. The patients with either idiopathic or ischemic cardiomyopathy were in New York Heart functional class II to IV and had a fractional myocardial shortening of <26% (assessed by echocardiography) at the time of evaluation. They had a left ventricular ejection fraction of <40% (as measured by radionuclide ventriculography) or a cardiac index of <3 liters/min/m^2 *(as determined by the thermodilution method), or both. They had no evidence of active infection, inflammatory disease, cancer, hypertension or renal failure. They received a standardized therapeutic regimen consisting of angiotensin-converting enzyme inhibitor, long-acting nitrates, digitalis, spironolactone and furosemide, the daily dose of which was titrated clinically and ranged from 40 to 250 mg/day. The histologic examination revealed hypertrophy of myocardial cells as the prominent feature in 66%, and extensive areas of replacement fibrosis with signs of myocardial cell degeneration in 33% of the IDC patients who underwent endomyocardial biopsy. Focal inflammatory infiltrates were additionally seen in 13%. Swan-Ganz right-sided cardiac catheterization, was performed simultaneously with blood sampling for assessment of immunologic, neurohumoral and clinical chemistry variables (Table 1). Native serum and ethylenediaminetetraacetate plasma were stored at –20°C until use. The serum levels of soluble interleukin-2 receptor and soluble CD4 were measured by enzyme-linked immunosorbent assay kits (Cellfree®, T Cell Sciences, Cambridge, Massachusetts) which were used according to the manufacturer's instructions. The plasma values of* β *2-microglobulin were determined by radioimmunoassay kits (Immunotech S.A., Marseille, France). Data are expressed as mean ± SEM; the p values are 2-tailed. A p value >0.05 was considered not significant. The significance of the differences between groups was evaluated by the 2-sample* t *test for unpaired data. Alternatively, the nonparametric Mann-Whitney U test was used, when large differences in group variances were evident in Hartley's F-max test. For simple linear regression between 2 variables the correlation coefficient r and the regression equation* $y = a + bx$ *with a as the intercept and b as the slope are reported. For polynomial regression of the second order the equation is* $y = a + bx + cx^2$*. The p values are 2-tailed for the probability that r and b are not equal to zero (*t *tests).*

TABLE II Characteristics of 36 Patients with Idiopathic Dilated Cardiomyopathy According to Plasma Concentration of Beta 2-Microglobulin

	Plasma Beta 2-Microglobulin*		
	High (n = 12)	Low (n = 24)	p Value
NYHA functional class (II/III+IV)	5/7	20/4	0.01
Furosemide daily dose (mg)	121 ± 47	21 ± 6	<0.01
Left ventricular ejection fraction†	0.1 ± 0.03 (n = 8)	0.24 ± 0.02 (n = 22)	<0.025
Serum sil-2R (U/ml)	750 ± 100	527 ± 41	<0.025
Serum soluble CD4 (U/ml)	25 ± 5	14 ± 2	<0.05
Plasma renin activity (ng/ml/hour)	26 ± 5	8 ± 2	<0.001
Serum sodium (mmol/liter)	140 ± 1	144 ± 1	<0.0025
Blood urea nitrogen (mg/dl)‡	23 ± 2	16 ± 1	<0.0005
Serum creatinine (mg/dl)§	0.9 ± 0.1	0.8 ± 0.1	NS
Serum bilirubin (mg/dl)‖	1.4 ± 0.3	0.7 ± 0.1	<0.005

*Plasma concentrations of ≥2.3 mg/liter (i.e., mean ± 2 SD of control group) were considered high, and those below this level were considered low.

†Left ventricular ejection fractions were determined by radionuclide ventriculography in the 30 patients with sinus rhythm; 6 patients with atrial fibrillation were excluded.

‡To convert values for blood urea nitrogen to mmol/liter of urea, multiply by 0.357.

§To convert values for creatinine to μM/liter, multiply by 88.4.

‖To convert values for bilirubin to μM/liter, multiply by 17.104.

NYHA = New York Heart Association; sil-2R = soluble interleukin-2 receptor.

Circulating β *2-microglobulin was slightly but significantly elevated in 36 patients with IDC compared with 30 age- and sex-matched control subjects (2.1 ± 0.1 vs 1.7 ± 0.1 mg/liter, p <0.005). The 1 IDC patients in New York Heart Association functional classes III and IV had higher plasma values than the 25 in New York Heart Association functional class II (2.7 ± 0.3 vs 1.8 ± 0.1 mg/liter, p <0.001). The clinical condition (i.e., New York Heart Association functional class, furosemide daily dosage) and left ventricular ejection fraction differed significantly between low and high level strata of* β *2-microglobulin (Table II). According to its physiologic role as a marker both of renal function and of T cell activation,* β *2-microglobulin reflected the stimulation of the renin-angiotensin system as well as T cellular hyperresponsiveness in IDC. On the one hand serum values of T cell markers (i.e., of soluble interleukin-2 receptor and soluble CD4) differed between IDC patients with low and high* β *2-micro-*

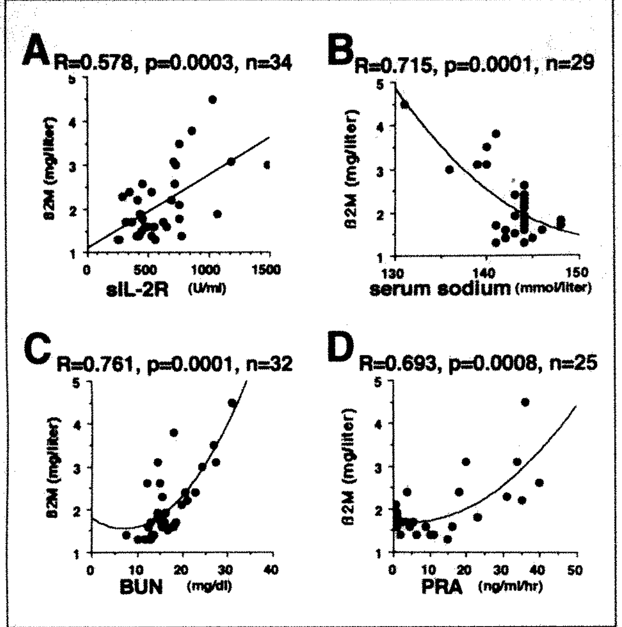

FIGURE 1. Correlation between circulating levels of beta 2-microglobulin (β2m) and those of: *A*, soluble interleukin 2-receptor (sIL-2R, $y = 1.1 + 0.002x$); *B*, serum sodium ($y = 149.6 - 1.9x + 0.006x^2$); *C*, blood urea nitrogen (BUN, $y = 1.8 - 0.07x + 0.005x^2$); and *D*, plasma renin activity (PRA, $y = 1.7 - 0.01x + 0.001x^2$).

globulin (Table II and Figure 1A). On the other hand, variables dependent on the renin-angiotensin system, (i.e., plasma renin activity, serum sodium and blood urea nitrogen, indicating the sequestration of "effective" volume into the third space) were different between low and high level strata of β 2- microglobulin (Table II) and correlated with the blood concentrations of β 2-microglobulin (Figure 1, B to D). Serum creatinine was loosely associated with plasma values of β 2-microglobulin ($r = 0.52$, $p = 0.0104$) between low and high responders (Table II). In the secondary form of chronic heart failure (i.e., ischemic cardiomyopathy), circulating β 2-microglobulin was also elevated above the normal range ($n = 19$, 2.3 ± 0.2 mg/liter, $p = 0.0001$). Specificity for myocardial diseases was demonstrated by the lack of enhanced release of β 2-microglobulin into the serum of patients with the non-mycoardial heart disease tested (i.e., coronary artery disease with normal left ventricular function [$n = 20$, 1.8 ± 0.1 mg/liter, p = not significant).

The results of this study confirm previous investigations, that the T cell-mediated immune response may play a role in the still unknown pathogenesis of IDC.[8–11] Our patients with IDC who had high circulating levels of β 2-microglobulin were in an advanced clinical stage and had higher serum values of other T cell markers than low β 2-microglobulin responders. Similarly, Samsonov et al[8] recently demonstrated serologic markers of T cell activation to be associated with the clinical condition in patients with IDC and chronic myocarditis. Elevated plasma β 2-microglobulin has likewise been demonstrated to be linked to disease progression in states of T cell stimulation (during viral infection,[2,3] lymphoproliferative and autoimmune disorders[4,5]).

Blood concentrations of β 2-microglobulin also depend on renal function, because >95% of this low molecular weight protein is excreted through the kidney by glomerular filtration supplemented by a peritubular mode of removal. Because of its marked retention in end-stage renal failure, β 2-microglobulin is the major conformational protein of dialysis-related amyloidosis that preferably involves articular and para-articular tissues.[7] Consequently plasma β 2-microglobulin reflected the renal function in our patient cohort with IDC: (1) There was a loose but significant correlation between circulating levels of β 2-microglobulin and those of creatinine. (2) Plasma β 2-microglobulin was closely linked with parameters of the stimulated renin-angiotensin system (i.e., increased plasma renin activity, high blood urea nitrogen and hyponatremia). This is in agreement with observations during and after cardiopulmonary bypass demonstrating that elevated plasma renin activity due to reduced renal perfusion correlates with urine concentrations of β 2-microglobulin.[12] In chronic heart failure the enhanced release of renin (with the concomitant increase of plasma β 2-microglobulin) indicates the overall hemodynamic stage. It is not only caused by the decreased renal blood flow, but also by the heightened adrenergic drive via adrenoceptors in the juxtaglomerular apparatus and by other mechanisms compensating the low cardiac output.[13]

In conclusion, the augmented circulating levels of β 2-microglobulin in IDC resulted from its enhanced synthesis by T lymphocytes as well as from its diminished clearance through the kidneys. Plasma β 2-microglobulin was associated both with the T cellular hyperresponsiveness and the stimulation of the renin-angiotensin-aldosterone axis in patients with IDC. Thus, β 2-microglobulin may serve as useful marker of disease activity, reflecting different aspects in the multifactorial pathogenesis of IDC. Future studies, directly performed on endomyocardial biopsy specimens, will have to prove if β 2-microglobulin also is an amyloidogenic protein in the failing heart according to its role in chronic renal insufficiency.[7]

Acknowledgment: We are grateful to Nora Gemeiner for excellent technical assistance, and to Michael Micksche, MD, for his generosity in allowing us the use of facilities at the Institute for Applied and Experimental Oncology, University of Vienna.

REFERENCES

1. Cresswell P, Springer T, Strominger JL, Turner MJ, Grey HM, Kubo RT. Immunological identity of a small subunit of HLA antigens and beta2-microglobulin and its turnover on the cell membrane. *Proc Natl Acad Sci USA* 1974; 71:2123–2127.

2. Cooper EH, Forbes MA, Hambling MH. Serum β_2-microglobulin and C reactive protein concentrations in viral infections. *J Clin Pathol* 1984;37:1140–1143.

3. Anderson RE, Lang W, Shiboski S, Royce R, Jewell N, Winkelstein W. Use of β_2-microglobulin level and CD4 lymphocyte count to predict development of acquired immunodeficiency syndrome in persons with human immunodeficiency virus infection. *Arch Intern Med* 1990;150:73–77.

4. Gertz MA, Kyle RA, Greipp PR, Katzmann JA, O'Fallon WM. Beta$_2$- microglobulin predicts survival in primary systemic amyloidosis. *Am J Cardiol* 1990; 89:609–614.

5. Litam P, Swan F, Cabanillas F, Tucker SL, McLaughlin P, Hagemeister FB, Rodriguez MA, Velasquez WS. Prognostic value of serum β-2 microglobulin in low-grade lymphoma. *Ann Intern Med* 1991;114:855–860.

6. Floege J, Wilks MF, Soose M, Kotzerke J, Shaldon S, Koch KM. Renal elimination of beta-2-microglobulin and myoglobin in patients with normal and impaired renal function. *Nephron* 1990;55:361–367.

7. Gejyo F, Odani S, Yamada T, Honma N, Saito H, Suzuki Y, Nakagawa Y, Kobayaski H, Maruyama Y, Hirasawa M, Suzuki M, Arakawa M. β2-Microglobulin: a new form of amyloid protein associated with chronic hemodialysis. *Kidney Int* 1986;30:385–390.

8. Samsonov M, Fuchs D, Reibnegger G, Belenkov JN, Nassonov EL, Wachter H. Patterns of serological markers for cellular immune activation in patients with dilated cardiomyopathy and chronic myocarditis. *Clin Chem* 1992;38:678–680.

9. Sanderson JE, Koch D, Iha D, Ojiambo HP. T-lymphocyte subsets in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1985;55:755–758.

10. Caforio ALP, Stewart JT, Bonifacio E, Burke M, Davies MJ, McKenna WJ, Bottazzo GF. Inappropriate major histocompatibility complex expression on cardiac tissue in dilated cardiomyopathy. Relevance for autoimmunity? *J Autoimmun* 1990;3:187–200.

11. Rudzite V, Jl Skards, Fuchs D, Reibnegger G, Wachter H. Serum kynurenine and neopterin concentrations in patients with cardiomyopathy. *Immunol Lett* 1992;32:125–130.

12. Canivet JL, Larbuisson R, Damas P, Blaffart F, Faymonville M, Limet R, Lany M. Plasma renin activity and urine beta 2-microglobulin during and after cardiopulmonary bypass: pulsatile vs non-pulsatile perfusion. *Eur Heart J* 1990,11:1079–1082.

13. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986;73:257–267.

Electrocardiographic Features of Atrial Tachycardias After Operation for Congenital Heart Disease

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and D. Woodrow Benson, Jr., MD, PhD

Atrial tachycardias occurring in young patients after surgery for congenital heart disease have been referred to as atrial flutter.[1–4] Typical atrial flutter is usually found in patients aged >50 years with coronary artery or hypertensive cardiovascular disease, or both.[5] Considering the different clinical setting for patients with typical atrial flutter[5] in contrast to patients after operation for congenital heart disease,[2–4] we evaluated the electrocardiographic features of atrial tachycardias in patients with postoperative congenital heart disease to see how many presented with typical atrial flutter.

Between 1983 and 1992, we evaluated 9 male and 21 female patients after operation for congenital heart disease who presented with sustained atrial tachycardia. At the time of tachycardia detection patients were 6 months to 48 years of age (mean 16 years, median 14). Table I lists the cardiac diagnoses and types of surgery performed. The time from operation until the tachycardia onset ranged from 3 days to 20 years (mean 7 years; median 9). Postoperative pacemaker implantation had been performed in 4 patients. At initial evaluation for tachycardia, 13 patients were not receiving any medication, 11 patients were receiving digoxin and 6 patients were receiving class I antiarrhythmic drugs. In this latter group, 2 patients were treated for atrial fibrillation (procainamide 1, quinidine 1) and 4 patients for atrial tachycardia (procainamide 3, quinidine 1). Antiarrhythmic drug blood concentrations at the time of the study were therapeutic in only 2 of 6 patients.

Presenting symptoms were palpitations (17 patients), dizziness (1 patient), nausea (1 patient) and lethargy (2 patients). Tachycardia was noted during routine checkup without symptoms in 9 patients.

The 12-lead electrocardiograms of the initial tachycardia episode were independently reviewed by 4 examiners and classified according to the 3 patterns described later. The classification was unanimous in 26 patients. In 4 patients the electrocardiogram was reviewed again in a blinded fashion and the majority vote accepted.

A bipolar esophageal electrocardiogram and standard electrocardiogram were recorded simultaneously at a paper speed of 50 and 100 mm/s to determine the atrial cycle length during tachycardia.

Since 24 patients eventually had tachycardia recurrence, a total of 104 tachycardia episodes was observed in the 30 patients. All episodes were converted with either temporary transesophageal pacing (95 episodes),[6] direct-current cardioversion (6 episodes), or by temporary rapid atrial pacing using an implanted DDD pacemaker (Medtronic Symbios 7005 for 3 episodes in 1 patient).

Based on observed electrocardiographic patterns, patients were classified into 3 groups. The distribution of atrial cycle lengths among the 3 groups is illustrated in Figure 1. Group 1 consisted of 9 patients (30%) with typical flutter waves in leads II, III and aVF, atrial cycle lengths of 160 to 260 ms (atrial rates of 231 to 375 beats/min) and 2:1 (3 patients), 3:1 (4 patients) and 4:1 (2 patients) conduction. Group 2 consisted of 10 patients (33%) with clearly detectable P waves present on the standard electrocardiogram that did not meet the criteria of flutter waves. Atrial cycle lengths were 140 to 380 ms (atrial rates of 158 to 375

TABLE I Diagnoses and Surgical Procedures in 30 Patients with Postoperative Sustained Atrial Tachycardia

Operation	No. of Pts.
Atrial baffle operation	
Simple d-TGA	5
Complex d-TGA	4
Fontan procedure	
Tricuspid atresia	4
Complex CHD	4
Definitive surgical procedures	
Ventricular septal defect	3
Atrial septal defect	2
Tetralogy of Fallot	1
Truncus arteriosus	1
Atrioventricular septal defect	1
Other complex congenital lesions	5

CHD = congenital heart disease; d-TGA = dextrotransposition of the great arteries.

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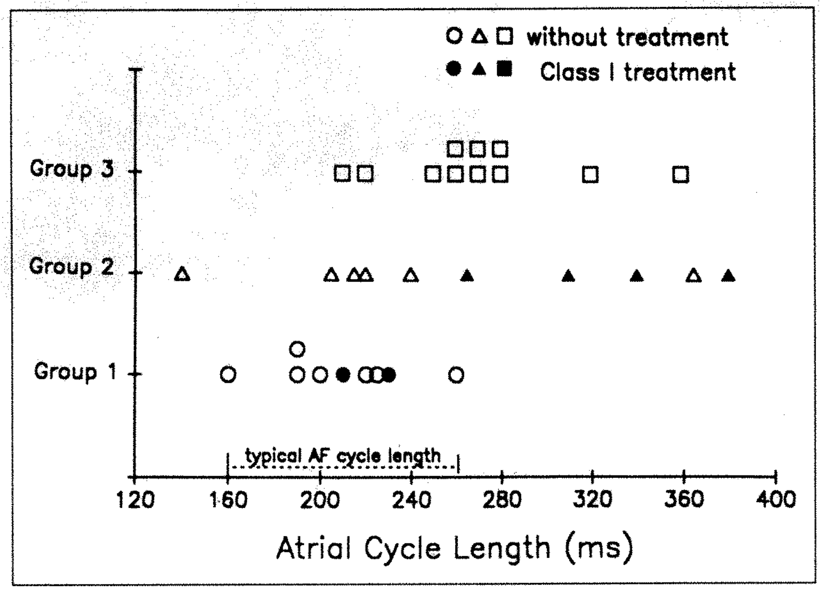

FIGURE 1. Distribution of atrial cycle lengths among 30 patients with postoperative congenital heart disease presenting with sustained atrial tachycardias.
AF = atrial fibrillation; Group 1 = flutter waves; Group 2 = clearly detectable P waves; Group 3 = no clearly visible P waves.

beats/min) with 1:1 (2 patients), 2:1 (7 patients) and 3:1 (1 patient) conduction. Group 3 consisted of 1 patients (37%) with no clearly visible P waves on the standard electrocardiogram. Atrial cycle lengths were 210 to 360 ms (atrial rates of 167 to 286 beats/min) with 1:1 (4 patients), 2:1 (6 patients) and 3:1 (1 patient) conduction. Figure 2 shows the different electrocardiographic features during tachycardia among the 3 groups. The atrial cycle lengths in patients treated with type I antiarrhythmic drugs overlapped with those of the untreated patients (Figure 1). Of the 2 patients with therapeutic blood concentrations of procainamide, 1 patient was in group 1 and 1 was in group 2. Of the other 4 patients receiving type I antiarrhythmic treatment, 1 patient was in group 1 and 3 were in group 2.

Although atrial tachycardias in patients with postoperative congenital heart disease are frequently referred to as atrial flutter, we found that 21 of 30 patients (70%) did not present the features of typical atrial flutter. To the extent that tachycardias can be characterized by electrocardiographic features and underlying heart disease, we suggest that atrial tachycardias in these young patients may differ from typical atrial flutter.

Typical or type I atrial flutter is associated with coronary artery or hypertensive cardiovascular disease, or both, in 2 of 3 of all cases, and in most cases patients are aged >50 years.[5] Studies in animals and humans[5,7–11] favor a reentrant mechanism, but the exact configuration of the reentrant circuit has not been completely defined. Boineau[7] emphasized the fundamental importance of the anatomic substrate including both caval orifices and a contiguous zone of myocardial discontinuity and slow conduction. Support for this idea was provided by Cosio et al[12] who demonstrated a circuit in the right posterior atrial wall rotating around the inferior vena cava in humans. However, Okumura et al[13] showed in a dog model that anatomic obstacles were not necessary. Nevertheless, there seems to be agreement about the need for a functional substrate in typical atrial flutter which is thought to consist of slow conduction or a repolarization inhomogeneity close to the potential reentrant circuit, or both.[7,12,13]

A variety of terms are used to describe "variants" of atrial flutter. Atypical atrial flutter describes a less common form, usually with slower atrial rates showing more discrete P waves and without sawtooth waves.[14] Boineau[7] described a spontaneous type II atrial flutter in a dog and correlated it to the atypical form of flutter in humans. Wells et al[15] described a type II atrial flutter in

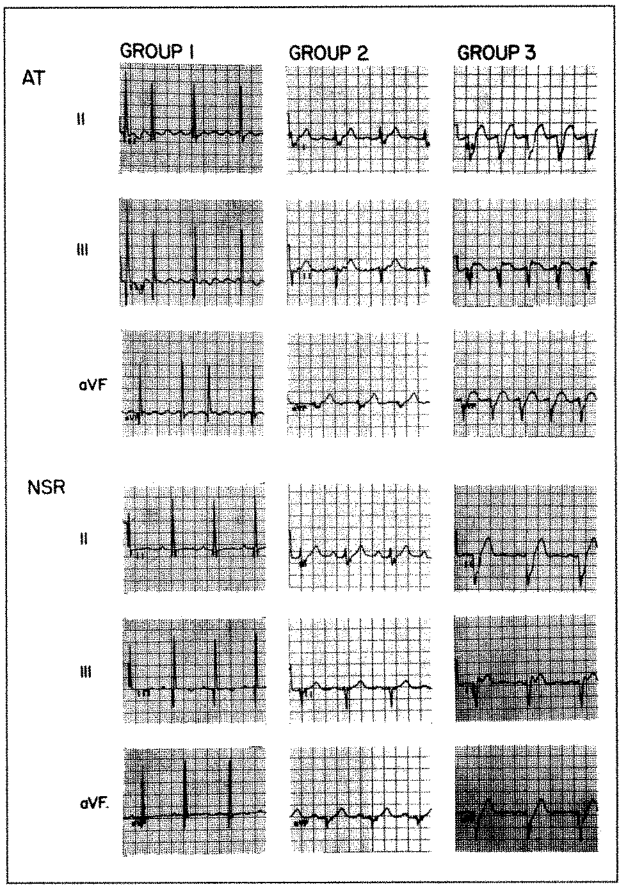

FIGURE 2. Standard electrocardiographic tracings II, III and aVF showing 3 different types of presentation of atrial tachycardias (AT) in patients with postoperative congenital heart disease before and after conversion to normal sinus rhythm (NSR).

humans with fast atrial rates distinct from uncommon or atypical atrial flutter, and suggested this type represented an intermediate form between type I flutter and atrial fibrillation. Some of the patients we evaluated had electrocardiographic features that would correspond to an "atypical" form of atrial flutter. However, some patients with atypical features had short tachycardia cycle lengths, and in 37% of patients no P waves were identified. Thus, as previously used, neither the term atypical, uncommon, or type II flutter seems sufficient to describe the tachycardias observed in the majority of patients reported in this study.

The anatomic substrate for atrial tachycardias after operation for congenital heart disease is thought to result from intraatrial surgery, cardiopulmonary bypass, myocardial scarring, and different zones of myocardial discontinuity unrelated to "normal" anatomic obstacles. These atrial tachycardias have been considered to be part of the tachycardia-bradycardia (sick sinus) syndrome.[1] Although damage to the sinus node has been hypothesized as the cause of these rhythm disturbances,[16] alteration in intraatrial conduction may be a more plausible explanation for observed tachycardia and bradycardia. Vetter et al[2] found intraatrial conduction delays and prolonged atrial refractoriness to be a frequent occurrence after the Mustard operation; 51% of patients had inducible intraatrial reentry tachycardia. Similarly, after the Fontan procedure, abnormalities of intraatrial conduction and refractoriness were frequently seen and 76% of patients had inducible intraatrial reentrant tachycardia.[3] In a dog model of the Mustard procedure, Shuman et al[17] found reentrant pathways involving suture lines and natural obstacles in different parts of the atria. These observations[2,3,17] as well as the high success rate of conversion with temporary pacing support the idea of a reentrant mechanism, although triggered activity as the electrophysiologic basis for tachycardias in this model of abnormal intraatrial conduction and refractoriness cannot be excluded.

The electrophysiologic basis and the mechanism of atrial tachycardias in the patients with postoperative congenital heart disease whom we studied is not completely known. However, since most of these young patients have a distinctive anatomic and functional substrate, it is not surprising that they do not have electrocardiographic features of typical atrial flutter. Instead, we suggest this entity be referred to as atrial tachycardia.

REFERENCES

1. Greenwood RD, Rosenthal A, Sloss LJ, LaCorte M, Nadas AS. Sick sinus syndrome after surgery for congenital heart disease. *Circulation* 1975;52:208–213.

2. Vetter VL, Tanner CS, Horowitz LN. Electrophysiologic consequences of the Mustard repair of d-transposition of the great arteries. *J Am Coll Cardiol* 1987;10:1265–1273.

3. Kürer CC, Tanner CS, Vetter VL. Electrophysiologic findings after Fontan repair of functional single ventricle. *J Am Coll Cardiol* 1991;17:174–181.

4. Garson A, Bink-Boelkens M, Hesslein PS, Hordof AJ, Keane JF, Neches WH, Porter CJ, and the other investigators of the Pediatric Electrophysiology Society. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol* 1985;6:871–878.

5. Watson RM, Josephson ME. Atrial flutter. I. Electrophysiologic substrates and modes of initiation and termination. *Am J Cardiol* 1980;45:732–741.

6. Butto F, Dunnigan A, Benditt DG, Benson DW Jr. Transesophageal study of recurrent atrial tachycardia after atrial baffle procedures for complete transposition of the great arteries. *Am J Cardiol* 1986;57:1356–1362.

7. Boineau JP. Atrial flutter: a synthesis of concepts. *Circulation* 1985;72:249–257.

8. Disertori M, Inama G, Vergara G, Guarnerio M, Del Favero A, Furlanello F. Evidence of a reentry circuit in the common type of atrial flutter in man. *Circulation* 1983;67:434–440.

9. Allessie MA, Lammers WJ, Bonke IM, Hollen J. Intraatrial reentry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. *Circulation* 1984;70:123–135.

10. Inoue H, Toda I, Saihara S, Sugimoto T. Further observations on entrainment of atrial flutter in the dog. *Am Heart J* 1989;118:467–474.

11. Inoue H, Matsuo H, Takayanagi K, Murao S. Clinical and experimental studies of the effects of atrial extrastimulation and rapid pacing on atrial flutter cycle. *Am J Cardiol* 1981;48:623–631.

12. Cosio FG, Arribas F, Barbero JM, Kallmeyer C, Goicolea A. Validation of doublespike electrograms as markers of conduction delay or block in atrial flutter. *Am J Cardiol* 1988;61:775–780.

13. Okumura K, Plumb VJ, Page PL, Waldo AL. Atrial activation sequence during atrial flutter in the canine pericarditis model and its effects on the polarity of the flutter wave in the electrocardiogram. *J Am Coll Cardiol* 1991;17:509–518.

14. Benditt DG, Benson DW Jr, Dunnigan A, Gornick CC, Anderson RW. Atrial flutter, atrial fibrillation, and other primary atrial tachycardias. *Med Clin North Am* 1984;68:895–918.

15. Wells JL, MacLean WAH, James TN, Waldo AL. Characterization of atrial flutter. Studies in man after open heart surgery using fixed atrial electrodes. *Circulation* 1979;60:665–673.

16. Gillette PC, Kugler JD, Garson A, Gutgesell HP, Duff DF, McNamara DG. Mechanisms of cardiac arrhythmias after the Mustard operation for transposition of the great arteries. *Am J Cardiol* 1980;45:1225–1230.

17. Shuman TA, Palazzo RS, Schuessler RB, Wolff GS, Boineau JP, Cox JL. Characterization of atrial flutter following the Mustard procedure for transposition of the great vessels (abstr). *J Am Coll Cardiol* 1991;17:209A.

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WARNINGS: ***Liver Dysfunction:*** **Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below.

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

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For more detailed information, consult your Merck Representative or see Prescribing Information.

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REFERENCES: List all authors, year, volume and inclusive pages for all journal references, and specific page numbers for all book references as shown below. Abstracts should not be used as references. Do not use periods after authors' initials or after abbreviations for titles of journals. Check *Index Medicus* or *Annals of Internal Medicine* (June 1982) as cited above for journal titles and abbreviations. Personal communications and unpublished observations do not constitute references, but may be mentioned within the text.

Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. *Am J Cardiol* 1984;53:900–915.

Chapter in Book: Cabot RC, White PD, Taussig HB, Levine SA, Wood P, Friedberg CK, Nadas AS, Hurst JW, Braunwald E. How to write cardiologic textbooks. In: Hope JA, ed. A Treatise on Disease of the Heart and Great Vessels. London: Yorke Medical Books, 1984:175–200.

Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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FROM THE EDITOR

Cardiologic Books Published in 1992

GENERAL CARDIOLOGY

*1. Willerson JT, editor, with 8 associate editors (Baim DS, Cooley DA, Frazier OH, Grundy SM, Kaplan NM, Packer M, Sweeney MS, Zipes DP). *Treatment of Heart Diseases.* New York: Gower Medical Publishing, 1992:528, $159.50.

Colorful and good.

*2. Loscalzo J, Creager MA, Dzau VJ, editors. *Vascular Medicine. A Textbook of Vascular Biology and Diseases.* Boston: Little, Brown and Company, 1992:1211, $165.00.

Excellent.

3. Cooke JP, Frohlich ED, editors. *Current Management of Hypertensive and Vascular Diseases.* St. Louis: B.C. Decker (An Imprint of Mosby Year Book), 1992:380, $79.00.

Good.

*4. Kapoor AS, Singh BN, editors. *Prognosis and Risk Assessment in Cardiovascular Disease.* New York: Churchill Livingstone, 1993:578, $79.95.

This book was designed to provide an authoritative source of current information for determining prognosis in major cardiovascular diseases. It appears to fulfill this mission. This is a very good book.

5. Marriott HJL. *Bedside Cardiac Diagnosis.* Philadelphia: JB Lippincott Company, 1993:291, $49.95.

Marriott makes the point in his preface that about 80% of cardiovascular diagnoses are made by history alone, another 10% require the physical examination, and only the remaining 10% are dependent on laboratory investigation. This good book of 40 relatively short chapters focuses on physical signs of cardiovascular disease. Good reading.

6. Chesler E. *Clinical Cardiology.* Fifth Edition. New York: Springer-Verlag, 1993:451, $89.00.

A bedside approach to cardiology. I would vote for the Marriott one.

7. Lilly LS, editor. *Pathophysiology of Heart Disease. A Collaborative Project of Medical Students and Faculty.* Philadelphia: Lea & Febiger, 1993:325, $24.50.

This book is a collaborative project of 38 Harvard Medical Students with faculty. The students, i.e., potential consumers, dissatisfied with currently available textbooks of cardiology, made their needs known. A useful book, particularly for the price.

8. Hillis LD, Lange RA, Wells PJ, Winniford MD. *Manual of Clinical Problems in Cardiology With Annotated Key References. Fourth Edition.* Boston: Little, Brown and Company, 1992:553, $28.00.

A useful book, particularly for house officers and cardiology fellows, and the price is right.

LIPIDS AND OTHER RISK FACTORS

9. Frishman WH, editor and coauthor. *Medical Management of Lipid Disorders: Focus on Prevention of Coronary Artery Disease.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:328, $60.00.

A very practical book.

10. Kreisberg RA, Segrest J, editors. *Plasma Lipoproteins and Coronary Artery Disease.* Boston: Blackwell Scientific Publications, 1992:390, $74.95.

Very good.

11. Thompson GR, Wilson PW. *Coronary Risk Factors and their Assessment.* London: Science Press, 1992: approximately 150, $60.00.

A colorful book. I prefer the Frishman one.

12. Goor R, Goor N. *Eater's Choice. A Food Lover's Guide to Lower Cholesterol. Third Edition.* Boston: Houghton Mifflin Company, 1992:571, $12.95.

This husband and wife team are cholesterol and nutrition experts. They have written several "best sellers" on this subject. I have liked all their books for adults (They have also written 7 childrens' books), and this one is no exception.

MEDICAL THERAPY

13. Ewy GA, Bressler R, editors. *Cardiovascular Drugs and the Management of Heart Disease. Second Edition.* New York: Raven Press, 1992:496, $105.00.

Fine book.

14. Taylor GJ. *Thrombolytic Therapy for Acute Myocardial Infarction.* Boston: Blackwell Scientific Publications, 1992:240, $24.95.

The price is right.

15. Opie LH. *Angiotensin-Converting Enzyme Inhibitors: Scientific Basis for Clinical Use.* New York: Wiley-Liss, 1992:266, $34.95.

Covers this topic well.

INTERVENTIONAL CARDIOLOGY

16. Vogel JHK, King SB III, editors. *The Practice of Interventional Cardiology, Second Edition.* St. Louis: Mosby Year Book, 1993:718, $95.00.

Good book.

17. Schwartz RS, editor. *Coronary Restenosis.* Boston: Blackwell Scientific Publications, 1993:387, $84.95.

Good book.

18. Serruys PW, Strauss BH, King SB III, editors. *Restenosis after Intervention with New Mechanical Devices.* Dordrecht: Kluwer Academic Publishers, 1992:504, $215.00.

A comprehensive assessment of restenosis from the perspective of new technologies including stenting, atherectomy, rotational abrasion, and lasers. At 42 cents a page, it is hardly worth it.

19. Ginsburg R, Geschwind HJ, editors. *Primer on Laser Angioplasty, Second Edition.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:520, $80.00.

For those interested in lasers, this is the book to have.

SYSTEMIC HYPERTENSION

20. Brunner HR, Waeber B, editors. *Ambulatory Blood Pressure Recording.* New York: Raven Press, 1992:192, $55.00.

Non-invasive ambulatory blood pressure recording is receiving progressively more attention since its beginning in about 1975. Over 300 publications on this subject appeared in 1990. This good small book nicely presents some of the problems and some benefits of ambulatory blood pressure monitoring.

*21. Loggie JMH, editor. *Pediatric and Adolescent Hypertension.* Boston: Blackwell Scientific Publications, 1992:416, $149.95.

Good.

22. Martinez-Maldonado M, editor. *Hypertension and Renal Disease in the Elderly.* Boston: Blackwell Scientific Publications, 1992:358, $79.95.

Nice book by outstanding contributors.

23. Cruickshank JM, Messerli FH. *Left Ventricular Hypertrophy and its Regression.* London: Science Press, 1992:107, $89.95.

In color. Not a lot of information. Almost a dollar a page!

CONGENITAL HEART DISEASE

*24. Freedom RM, Benson LN, Smallhorn JF, editors. *Neonatal Heart Disease.* London: Springer-Verlag, 1992:881, $180.00.

This book will probably be the bible for information on the newborn with heart disease. Although an edited book, one or more of the editors are authors of nearly all chapters.

25. Rao PS, editor. *Tricuspid Atresia. Second Edition.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:458, $98.00.

The first edition appeared just over 10 years ago. I like these comprehensive books on a single topic and that is what this one is.

26. Hess J, Sutherland GR, editors. *Congenital Heart Disease in Adolescents and Adults.* Dordrecht: Kluwer Academic Publishers, 1992:201, $100.00.

There are better ones on this subject.

ARRHYTHMIAS, ELECTROCARDIOGRAPHY, ELECTROPHYSIOLOGY, PACING, DEFIBRILLATORS

*27. Josephson ME, Second Edition. *Clinical Cardiac Electrophysiology: Techniques and Interpretations.* Philadelphia: Lea & Febiger, 1993:839, $95.00.

A must for students of this field. Josephson wrote every word. Outstanding.

28. Singer I, Kupersmith J, editors. *Clinical Manual of Electrophysiology.* Baltimore: Williams & Wilkins, 1993:453, $60.00.

Very few illustrations. Josephson a winner hands down.

29. Wit AL, Janse MJ. *The Ventricular Arrhythmias of Ischemia and Infarction. Electrophysiological Mechanisms.* Mount Kisco, NY: Futura Publishing Company, Inc., 1993:648, $150.00.

A fine book BUT the Josephson one is 37% less expensive and contains 23% more pages which are also larger.

30. Seelig CB. *Simplified EKG Analysis. A Sequential Guide to Interpretation and Diagnosis.* Philadelphia: Hanley & Belfus, Inc., 1992:119, $14.95.

31. Stein E. *Rapid Analysis of Electrocardiograms. A Self-Study Program. Second Edition.* Philadelphia: Lea & Febiger, 1992:404, $26.95.

32. Stein E. *Rapid Analysis of Arrhythmias. A Self-Study Program. Second Edition.* Philadelphia: Lea & Febiger, 1992:229, $24.95.

33. Kingma JH, van Hemel NM, Lie KI, editors. *Atrial Fibrillation, a Treatable Disease?* Dordrecht: Kluwer Academic Publishers, 1992:297, $99.00.

A hot topic. Content per page could have been more.

34. Luceri RM, editor. *Sudden Cardiac Death: Strategies for the 1990s.* Miami Lakes, Florida: Peritus Corporation, 1992:194, $60.00.

This book represents a collection of manuscripts concerning primarily implantable cardioverter-defibrillators and both the symposium and this publication are underwritten by Telectronics Pacing Systems. Not recommended.

35. Ellenbogen KA, editor. *Cardiac Pacing.* Boston: Blackwell Scientific Publications, 1992:464, $29.95.

A very good book for the money. Highly recommended.

ECHOCARDIOGRAPHY

*36. Silverman NH. *Pediatric Echocardiography.* Baltimore: Williams & Wilkins, 1993:628, $140.00.

Superb book. Loaded with fine illustrations.

37. Obeid AI. *Echocardiography in Clinical Practice.* Philadelphia: JB Lippincott Company, 1992:383, $125.00.

A large book loaded with 2-dimensional, Doppler, and transesophageal images. The images should have been cropped and then they could have been reproduced much larger. Nevertheless, the reproductions are excellent. A useful book.

*38. Nanda NC, editor. *Doppler Echocardiography. Second Edition.* Philadelphia: Lea & Febiger, 1993:466, $129.00.

Beautiful book. Illustrations are splendid. Probably the best so far on this subject.

39. Labovitz AJ, Williams GA. *Doppler Echocardiography. The Quantitative Approach. Third Edition.* Philadelphia: Lea & Febiger, 1992:131, $29.95.

This third edition appears only 5 years after the first edition. It incorporates real-time flow mapping techniques into the text. The illustrations are superb.

40. Oka Y, Goldiner PL, editors. *Transesophageal Echocardiography.* Philadelphia: JB Lippincott Compa-

ny, 1992:338, $150.00.

Nice book but a good bit of wasted space. Photographs could have been cropped.

41. Missri J. *Transesophageal Echocardiography. Clinical and Intraoperative Applications.* New York: Churchill Livingstone, 1993:248, $124.95.

Good.

42. Dittrich HC, editor. *Clinical Transesophageal Echocardiography.* St. Louis: Mosby Year Book, 1992:178, $95.00.

An edited book with 22 contributors.

43. Labovitz AJ, Pearson AC. *Transesophageal Echocardiography: Basic Principles and Clinical Applications.* Philadelphia: Lea & Febiger, 1993:157, $39.50.

Good.

INTRAVASCULAR ULTRASOUND IMAGING

44. Tobis JM, Yock PG, editors. *Intravascular Ultrasound Imaging.* New York: Churchill Livingstone, 1992:262, $89.95.

Probably the best so far on this subject.

45. Cavaye DM, White RA. *Intravascular Ultrasound Imaging.* New York: Raven Press, 1993:119, $59.00.

Good but short and relatively expensive. Good reproductions.

CARDIAC IMAGING

46. Jay ME. *Plain Film in Heart Disease.* Boston: Blackwell Scientific Publications, 1992:207, $34.95.

This book is loaded with chest roentgenograms with brief case presentations. The space on the pages is poorly utilized. The book which is already relatively small could have been much smaller.

47. van der Wall E, Sochor H, Righetti A, Niemeyer MG. *What's New in Cardiac Imaging? SPECT, PET, and MRI.* Dordrecht: Kluwer Academic Publishers, 1992:544, $149.00.

48. van der Wall EE. *Nuclear Cardiology and Cardiac Magnetic Resonance. Physiology, Techniques and Applications.* Leiden, The Netherlands: Hans Soto Productions, 1992:285, $115.00.

49. Wagner M, Lawson TL. *Atlas of Chest Imaging. Correlated Anatomy with MRI and CT.* New York: Raven Press, 1992:134, $80.00.

The use of abbreviations in titles is not ideal. Over half of the pages utilize only a half of the page. The book could have been much smaller and that would have made it better. The reader is not getting his/her money's worth here.

50. Stanford W, Rumberger JA, editors. *Ultrafast Computed Tomography in Cardiac Imaging: Principles and Practice.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:351, $80.00.

A useful book.

*51. Bregmann SR, Sobel BE, editors. *Positron Emission Tomography of the Heart.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:313, $98.00.

I suspect that this book is the best one on this subject.

CARDIOVASCULAR SURGERY

*52. Kirklin JW, Barratt-Boyes BG, with the collaboration of Blackstone EH, Jonas RA, Kouchoukos NT. *Cardiac Surgery. Morphology, Diagnostic Criteria, Natural History, Techniques, Results, and Indications. Second Edition. Volumes 1 and 2.* New York: Churchill Livingstone, 1993:1860, $250.00.

This book is by far the best on this subject.

53. Bojar RM. *Adult Cardiac Surgery.* Boston: Blackwell Scientific Publications, 1992:562, $99.95.

This book does not include congenital heart lesions except for the congenitally malformed aortic valve, mitral valve prolapse, hypertrophic cardiomyopathy, and the Marfan syndrome seen in adulthood. This book by a single author is both good and useful, but can hardly compete with the Kirklin-Barratt-Boyes one!

54. Bharati S, Lev M, Kirklin JW. *Cardiac Surgery and the Conduction System. Second Revised Edition.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:159, $75.00.

This book primarily presents drawings and some gross pictures of views of the heart as might be seen at operation with delineation of courses of the conduction system in various types of congenital anomalies of the heart. The text is brief. Much empty space is present on the pages. This book is important because of the authors.

55. Kotler MN, Alfieri A, editors. *Cardiac and Noncardiac Complications of Open Heart Surgery: Prevention, Diagnosis, and Treatment.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:418, $62.00.

A useful book, interestingly edited by 2 cardiologists. Very little emphasis is given to mechanical or anatomic complications of cardiac surgery. Certainly they are not as important in the 1990s as they were in the 1960s but they remain important.

56. Engelman RM, Levitsky S, editors. *A Textbook of Cardioplegia for Difficult Clinical Problems.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:334, $75.00.

As Frank C. Spencer states in the Preface: ". . . the book is an excellent description of the wide variety of methods of cardioplegia used for the most difficult clinical problems throughout the world. This wide variation indicates that no one method has evolved as superior to another."

57. Kay PH, editor. *Techniques in Extracorporeal Circulation, Third Edition.* Oxford, UK: Butterworth-Heinemann Ltd., 1992:336, $195.00.

The first edition of this book appeared 16 years ago, and the second edition 11 years ago. Thus, it is time for an update and this was nicely accomplished by 45 authors.

58. Ross DN, English TAH, McKay R. *Principles of Cardiac Diagnosis and Treatment. A Surgeons' Guide. Second Edition.* London: Springer-Verlag, 1992:269,

$129.00.

The first edition appeared in 1962, thirty years earlier. This book is pleasant reading but at nearly 50 cents a page, it's not worth it.

PERIPHERAL VASCULAR DISEASE

59. Polak JF. *Peripheral Vascular Sonography. A Practical Guide.* Baltimore: Williams & Wilkins, 1993:364, $78.00.

Good for this subject.

60. Dorros G. *Peripheral Vascular Interventions 1992. A Bibliographic Reference Manual.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:438, $80.00.

What it says it is, it is, a bibliography with some summaries. For those in this field, it may be useful.

61. Clement DL, Shepherd JT, editors. *Vascular Diseases in the Limbs. Mechanisms and Principles of Treatment.* St. Louis: Mosby Year Book, 1993:319, $79.00.

Well done.

MOLECULAR CARDIOLOGY

*62. Roberts R, editor. *Molecular Basis of Cardiology.* Boston: Blackwell Scientific Publications, 1993:518, $39.95.

As Eugene Braunwald states in the foreword, *Molecular Basis of Cardiology* is the best exposition of this new paradigm (the shift in cardiovascular science from organ physiology to molecular biology) currently available and will be of enormous value to cardiovascular scientists, scholarly cardiologists, and to new entrants in the field. The publisher provided the book in soft cover to keep the price reasonable.

63. Gotto AM, Jr, editor. *Cellular and Molecular Biology of Atherosclerosis.* London: Springer-Verlag, 1992:180, $83.00.

This book represents presentations at the 1991 Princess Lillian Symposium, which I attended. The presentations were good and their publication is better.

MISCELLANEOUS

*64. Katz AM. *Physiology of the Heart. Second Edition.* New York: Raven Press, 1992:687, $55.00.

The first edition was 1977. Thus, this second one is long overdue. This second edition is essentially an entirely new text.

65. Pashkow FJ, Dafoe WA, editors. *Clinical Cardiac Rehabilitation: A Cardiologist's Guide.* Baltimore: Williams & Wilkins, 1993:391, $59.00.

Good.

66. Anderson RH, Becker AE. *The Heart. Structure in Health and Disease.* London: Gower Medical Publishing, 1992:266, $165.00.

This book is a consolidation and expansion of their 2 previous books with Gower Medical Publishing, namely *Cardiac Anatomy* (1980) and *Cardiac Pathology* (1983). The pictures are in color. A beautiful book.

67. Yellon DM, Jennings RB, editors. *Myocardial Protection. The Pathophysiology of Reperfusion and Reperfusion Injury.* New York: Raven Press, 1992:214, $99.00.

This concise book on an important subject will be useful. The cost, however, is nearly 50 cents a page.

68. Fowles RE, editor. *Cardiac Biopsy.* Mount Kisco, NY: Futura Publishing Company, Inc., 1992:211, $47.00.

For anyone performing or examining biopsies of the heart, this is a good book to have.

69. Kaye D, editor. *Infective Endocarditis, Second Edition.* New York: Raven Press, 1992:497, $85.00.

This book is a follow-up of Kaye's first edition in 1976. The first edition emphasized the effects of antibiotics on infective endocarditis. The present edition, a considerable expansion from the first, continues to emphasize further changes in the disease including an older age of patients, less rheumatic heart disease, less pneumococcal and gonococcal endocarditis, more staphylococcal endocarditis, the increasing frequency in intravenous drug abusers, the problems of prosthetic and bioprosthetic endocarditis, the usefulness of echocardiography, and many management changes. This book is highly recommended.

CARDIOLOGIC ANNUALS

70. Roberts WC, Willerson JT, Mason DT, Rackley CE, Graham TP Jr. *Cardiology 1992.* Boston: Butterworth-Heinemann, 1992:480, $80.00.

71. Schlant RC (editor in chief), Collins JJ Jr, Engle MA, Frye RL, Kaplan NM, O'Rourke RA (editors). *Year Book of Cardiology 1992.* St. Louis: Mosby Year Book, 1992:441, $59.95.

The Schlant book, the thirty-second in the series, contains summaries and comments on 318 articles plus 111 figures and 5 tables. The Roberts book, the twelfth in the series, contains summaries of 740 articles plus 116 figures and 32 tables. The Roberts book provides 58% more summaries of articles than does the Schlant book on only 8% more pages because each page contains far more content. The cost of the Roberts book, however, is 30% higher than the Schlant book, and it lacks editorial comments from the editors on each article summarized.

COMMENTS

More and more cardiologic books! The first column I wrote on cardiologic books summarized those appearing in 1985 and it briefly discussed 16 books,[1] and the column in 1991 described 49 books.[2] The present piece discusses 71 books, 53 (75%) of which have a 1992 publication date and 18 (25%) of which have a 1993 publication date. The books marked with asterisks are those which I consider noteworthy either because of extremely high quality or uniqueness.

The costs of books continue to increase. The prices of the 71 books appearing in 1992 ranged from $12.95 to $250.00 (mean $88.39). The numbers of pages in the

71 books ranged from 119 to 1860 (mean 405). There was an insignificant relation between the number of pages a book contained and its cost. The total cost of the 71 books was $6,275.50 and the total numbers of pages in the 71 books was 28,835. Therefore, the average cost of each page was 22 cents.

Of the 71 books, 38 (55%) were edited with multiple contributors, and 33 (45%) were by 1 to 6 authors. Only 15 books (21%) had a single author.

Most books unfortunately continue to be published on acid paper.[3] Of the 71 books, only 9 (13%) were published on acid-free paper, i.e., permanent paper. The remaining 62 books (87%) will vanish into dust within 50 years. Congratulations to Butterworth-Heinemann, Kluwer Academic, and Springer-Verlag for publishing all of their books on acid-free paper, and to Futura for publishing some of their books on alkaline paper. I encourage all authors to require in their book contracts that the paper used for their books be acid-free. It is time for American book publishers to use permanent paper!

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

REFERENCES

1. Roberts WC. Some good cardiologic books. *Am J Cardiol* 1985;56:1001–1002.

2. Roberts WC. Some good cardiologic books published in 1991. *Am J Cardiol* 1992;69:141–144.

3. Roberts WC. Alkaline paper and preserving the record. *Am J Cardiol* 1991; 68:1729–1732.

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Specifically, FDA has stated that Hoechst-Roussel's advertising and promotional materials:

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(2) made false statements and implications that certain patients who receive generic furosemide in substitution for Lasix may not be receiving the care they need; and

(3) made false statements and suggestions that Lasix is superior to generic furosemide products.

FDA has concluded that there is inadequate data to substantiate these promotional claims.

All FDA-approved dosage forms of furosemide oral tablets, including those manufactured by Hoechst-Roussel, are "AB" rated. According to FDA's coding system, products coded "AB" under an ingredient- and dosage-form heading are considered therapeutically equivalent to other products coded "AB" under that heading and are considered appropriate for substitution.

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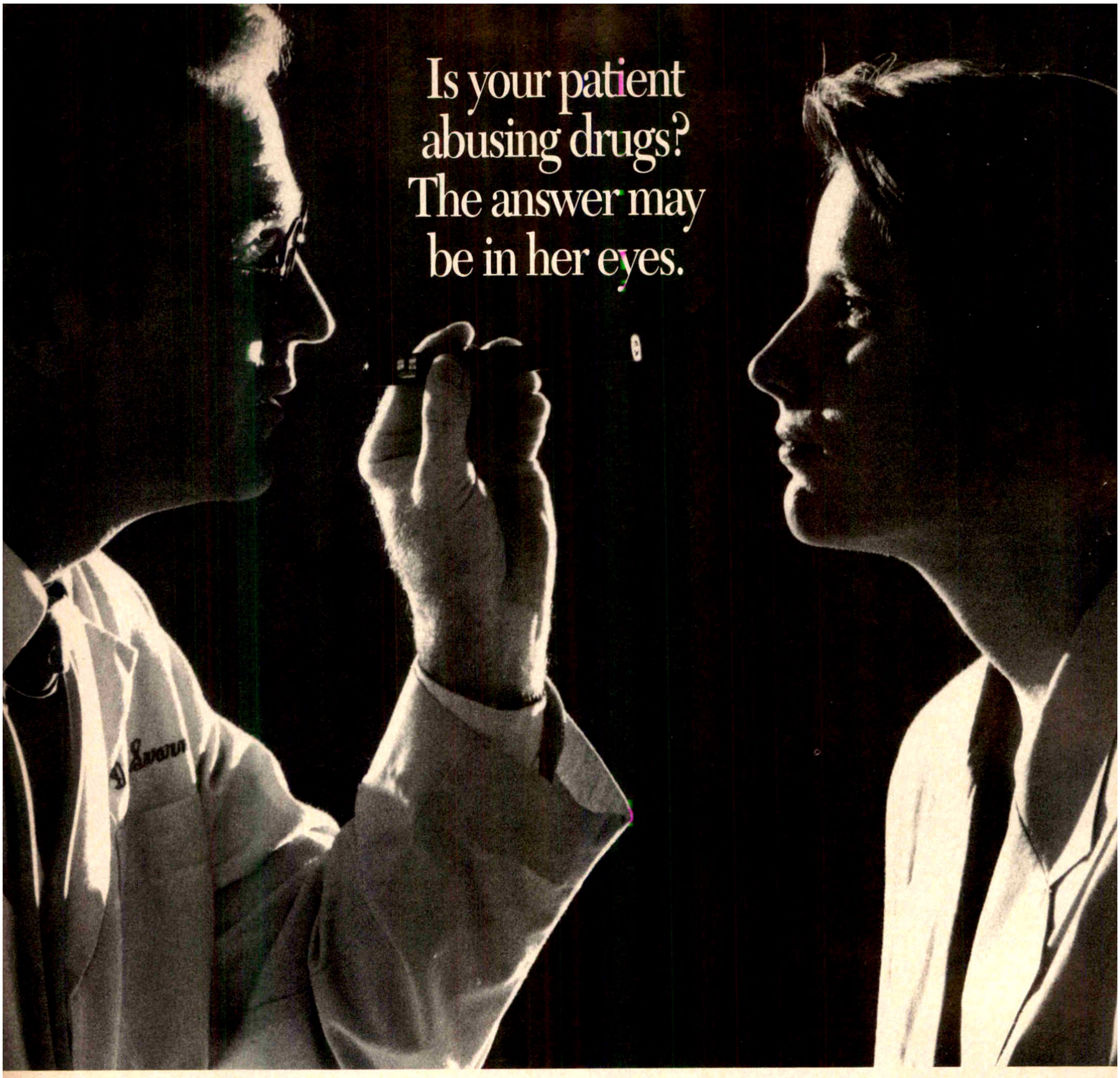
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Pupil reaction	Slow, sluggish, or absent response
Nystagmus	Failure to hold gaze; Jerkiness of movements
Convergence	Inability to track or hold the cross-eyed position
Corneal reflex	Decreased rate of blinking

Tennant F. The rapid eye test to detect drug abuse. *Postgrad Med.* 1988;84:109-114.

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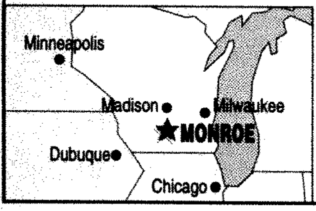

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Contact: Carl V. Leier, M.D., Division of Cardiology
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JANUARY, 1993

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The publisher is not responsible for any errors or omissions.

Lopressor®
metoprolol tartrate USP

Tablets
Ampuls

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension

Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction

Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS**, and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction

Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General

Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS**, and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD$_{50}$'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Printed in U.S.A. C90-39 (Rev. 7/90)

Geigy
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Ardsley, New York 10502

1. 1988 Joint National Committee. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1988;148:1023-1038.

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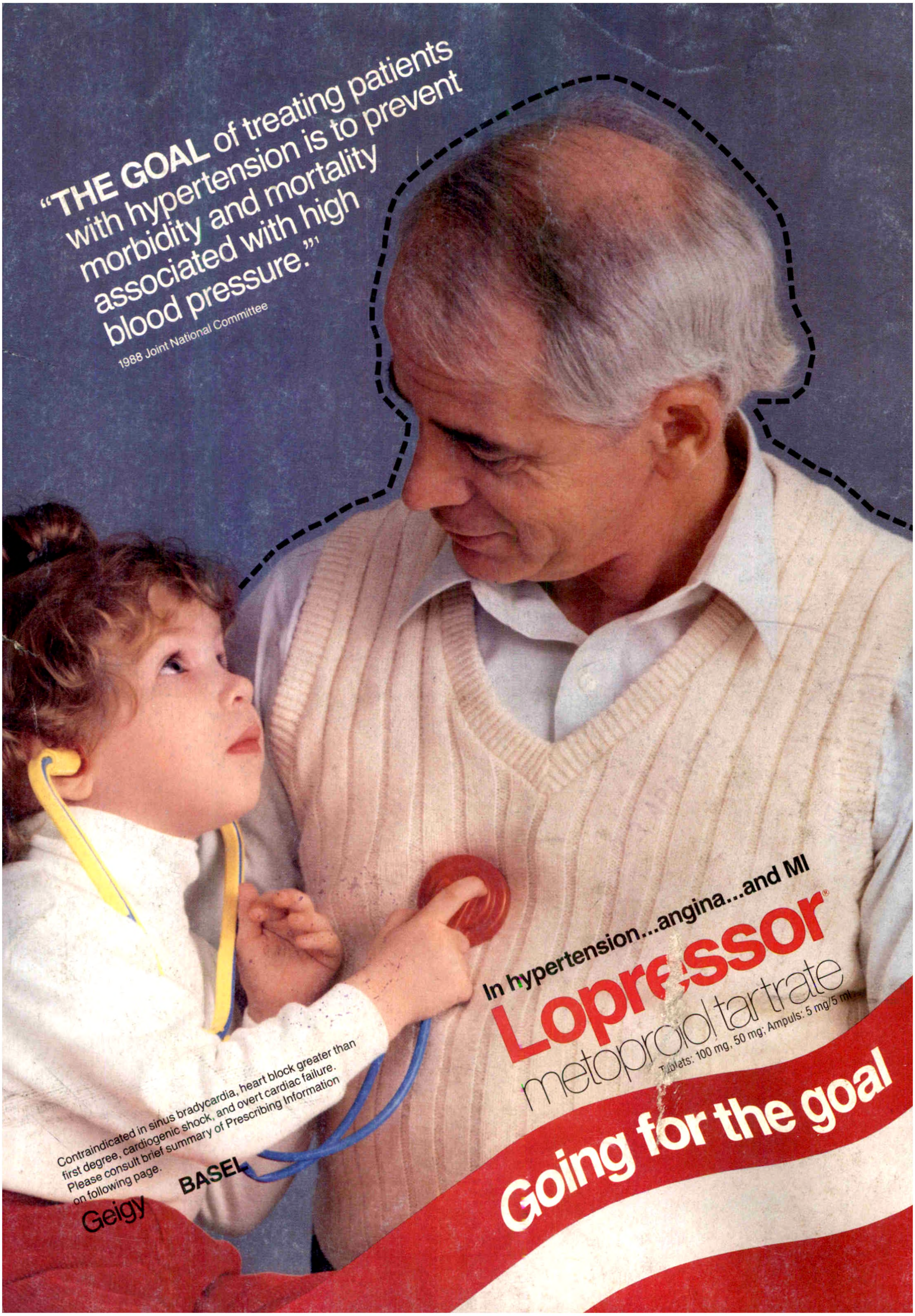

"**THE GOAL** of treating patients with hypertension is to prevent morbidity and mortality associated with high blood pressure."[1]

1988 Joint National Committee

In hypertension...angina...and MI

Lopressor®

metoprolol tartrate

Tablets: 100 mg, 50 mg; Ampuls: 5 mg/5 ml

Going for the goal

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. Please consult brief summary of Prescribing Information on following page.

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JANUARY 15, 1993

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Triad patients are at increased risk of heart attack[1,2]

In the placebo population of the Helsinki Heart Study, patients with the triad of risk—low HDL, elevated LDL, and elevated triglycerides—have been shown to be almost four times more likely to develop CHD.[1]

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CHDetour:

LOPID reduced CHD[*] by 57% in triad patients[†]

In the Helsinki Heart Study, LOPID reduced heart attack by 57% in patients at very high risk and by 34% overall.[‡] LOPID raises HDL and lowers LDL and triglycerides while it reduces the risk of developing CHD as an adjunct to diet in patients with the triad of lipid abnormalities who have had an inadequate response to exercise, dietary therapy, weight loss, and trial of other pharmacologic agents (such as bile acid sequestrants and nicotinic acid).

LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in type IIb patients who are without history of or symptoms of existing coronary heart disease **and** who have the following triad of lipid abnormalities: low HDL cholesterol in addition to elevated LDL cholesterol and elevated triglycerides.

In addition, the potential benefit of gemfibrozil in treating type IIa patients with elevations of LDL cholesterol only is not likely to outweigh the risks. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

57%

LOPID®

(gemfibrozil) 600-mg Tablets BID

TREATS THE TRIAD

REDUCES THE RISK OF DEVELOPING CHD

With baseline HDL above the median (46.4 mg/dL), the incidence of serious coronary events was similar for LOPID and placebo groups.

Defined as a combination of definite coronary death and/or definite myocardial infarction. 57% calculated from an incidence of CHD of 149/1000 among placebo patients and 64/1000 among treated patients.

Baseline LDL >175 mg/dL, baseline TG >200 mg/dL, and baseline HDL <35 mg/dL.

All patients were counseled on dietary therapy and encouraged to exercise and quit smoking.

Please see adjacent page for brief summary of prescribing information.

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LOPID®

(gemfibrozil) 600-mg Tablets BID

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. See CLINICAL PHARMACOLOGY section in full prescribing information which includes the following: The secondary prevention component of the Helskinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, $p=0.14$). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the Lopid group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, $p=0.06$). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients *without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20	Bottles of 60
N 0071-0737-30	Bottles of 500
N 0071-0737-40	Unit dose packages of 100 (10 strips of 10 tablets each)

Parcode® No. 737

Storage: Store below 30° C (86° F).

REFERENCES

1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245.
2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651.
3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury JB et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.
4. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988;148:36-39.

Caution – Federal law prohibits dispensing without prescription.

0737G015

Revised April 1992

REFERENCES:

1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.
2. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). *Am J Cardiol.* 1992;70:733-737.

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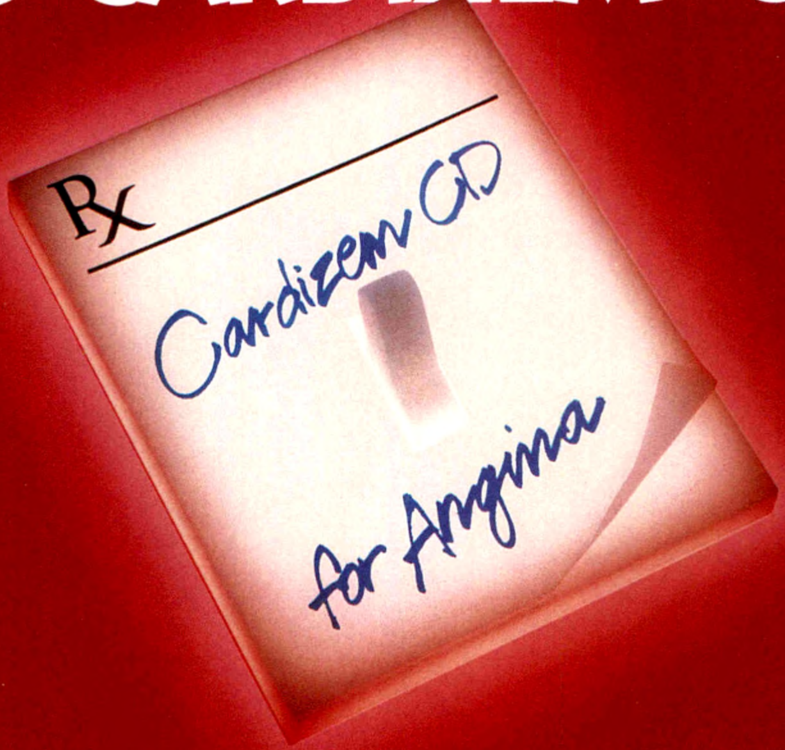

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CCDAH828/A7514

1025S2

ONCE ADAY

Now for both angina and hypertension

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

Switch from Cardizem (diltiazem HCl) tablets on a total mg/day basis*

For new patients, a recommended starting dose:

- One 180-mg capsule qd

*Monitor and titrate.

Brief Summary of
Prescribing Information as of October 1992 (2)
CARDIZEM® CD
(diltiazem hydrochloride)
Capsules

Brief Summary of
Prescribing Information as of January 1991
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules

Brief Summary of
Prescribing Information as of January 1991
CARDIZEM®
(diltiazem hydrochloride)
Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

Double Blind Placebo-Controlled Hypertension Trials

Adverse	Diltiazem N = 315 # pts (%)	Placebo N = 211 # pts (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	---
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	---

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsules Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reaction	CARDIZEM CD N = 607	Placebo N = 301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%). In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

CARDIZEM® CD
Prescribing Information as of October 1992 (2)

CARDIZEM® SR
Prescribing Information as of January 1991

CARDIZEM®
Prescribing Information as of January 1991

Marion Merrell Dow Inc.
Kansas City, Missouri 64114

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

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1025R2

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JANUARY 15, 1993, VOL. 71, NO. 2

CORONARY ARTERY DISEASE

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Impact of Treatment Strategy on Predischarge Exercise Test in the Thrombolysis in Myocardial Infarction (TIMI) II Trial

Bernard R. Chaitman, Robert P. McMahon, Michael Terrin, Liwa T. Younis, Leslee J. Shaw, Donald A. Weiner, Margaret M. Frederick, Genell L. Knatterud, George Sopko, and Eugene Braunwald, for the TIMI Investigators

Predischarge supine bicycle ergometry was used to assess residual postinfarct myocardial ischemia in patients who received thrombolytic therapy in the TIMI II trial. One-year mortality was greater in patients who did not perform the predischarge exercise test than in those who did ($p < 0.001$); the former were older ($p < 0.001$), and a greater proportion were women ($p < 0.001$), and had a more frequent history of myocardial infarction ($p < 0.01$), and more extensive coronary artery disease ($p < 0.001$). One-year mortality in patients with exercise-induced ST-segment depression or chest pain was only 1.4% in those randomly assigned to the conservative strategy and 2.5% in those randomly assigned to the invasive strategy. In postinfarct patients treated with thrombolytic therapy and a conservative strategy, the recommendation of performing cardiac catheterization and coronary revascularization when the predischarge exercise test is abnormal results in a low 1-year mortality for those with exercise-induced angina or ST-segment depression, which is comparable to that for patients who do not have this finding.

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Transient Myocardial Ischemia After a First Acute Myocardial Infarction and Its Relation to Clinical Characteristics, Predischarge Exercise Testing and Cardiac Events at One-Year Follow-Up

Hans Mickley, Peter Pless, Jens R. Nielsen, Jens Berning, and Mogens Møller

The relation between early postdischarge ambulatory ST-segment monitoring, clinical characteristics, predischarge maximal exercise testing and cardiac events was determined in 123 consecutive men <70 years old with a first acute myocardial infarction. During 36 hours of ambulatory recording 11 days after acute myocardial infarction, 23 patients (19%) demonstrated ischemia (group 1), whereas 100 patients did not (group 2). Exercise-induced ischemia was significantly more prevalent and severe in group

1 patients, who also demonstrated a limited hemodynamic response. During 1-year follow-up, the frequency of cardiac events (cardiac death, nonfatal reinfarction, severe angina) was 52% in group 1, which was significantly higher than the 22% found in group 2. Exercise-induced ischemia did not predict outcome: event rate 30% in group 1 vs 25% in group 2. None of the 5 patients who died within 1 year had ischemia during any of the electrocardiographic methods. However, a significant association between a low left ventricular ejection fraction and 1-year mortality was found.

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Continuously Updated 12-Lead ST-Segment Recovery Analysis for Myocardial Infarct Artery Patency Assessment and Its Correlation with Multiple Simultaneous Early Angiographic Observations

Mitchell W. Krucoff, Martha A. Croll, James E. Pope, Karen S. Pieper, Prapti M. Kanani, Christopher B. Granger, Rolf F. Veldkamp, Beverly L. Wagner, Sharon T. Sawchak, and Robert M. Califf

Continuous 12-lead ST-segment monitoring was analyzed in 22 patients with acute myocardial infarction undergoing early angiography. ST-recovery analysis at the moment of angiography was 90% sensitive and 92% specific for detection of an occluded infarct vessel. Despite this strong instantaneous correlation, cumulative speed, stability and duration of ST recovery over time did not correlate across patients subgrouped by angiographic patency. In 50% of patients, multiple ST-trend transitions suggested cyclic changes in coronary patency before angiography. Cumulative parameters of ST-segment recovery, as proposed in this study, probably reflect the speed, stability and duration of reperfusion, including quantification of cyclic changes in coronary flow before, during and after angiography.

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Frequency and Prognostic Significance of Secondary Ventricular Fibrillation Complicating Acute Myocardial Infarction

Solomon Behar, Henrietta Reicher-Reiss, Michael Shechter, Babeth Rabinowitz, Elieser Kaplinsky, Edward Abinader, Jacob Agmon, Yaacov Friedman, Jacob Barzilai, Nissim Kauli, Yehezkiel Kishon, Abraham Palant, Benyamin Peled, Leonardo Reisin, Zwi Schlesinger, Izhar Zahavi, Monty Zion, and Uri Goldbourt, for the SPRINT Study Group

The incidence of secondary ventricular fibrillation (VF) complicating acute myocardial infarction was 2.4% in a large cohort of unselected patients with acute myocardial infarction. In-hospital mortality was significantly higher than in patients without VF. Multivariate analysis showed that secondary VF is an independent predictor of higher in-hospital death. The mortality 5 years after discharge was similar in patients with and without secondary VF during hospitalization.

Continued on page A15

THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...

NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

THE CARDURA

[*] Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in th various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg; and acebutolol (400 mg/day), 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

[†] n=128; $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decreas in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

[‡] Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION

Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)[*] in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

[§] These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets
1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary on last page.

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ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets
1 mg, 2 mg, 4 mg, 8 mg

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

HYPERTENSION CONTROL
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Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue / malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	
	Muscle Weakness	1%	
	Myalgia	1%	
CENTRAL & PERIPHERAL N.S.:	Headache	14%	1
	Paresthesia	1%	1
	Kinetic Disorders	1%	
	Ataxia	1%	
	Hypertonia	1%	
	Muscle Cramps	1%	
AUTONOMIC:	Mouth Dry	2%	
	Flushing	1%	
SPECIAL SENSES:	Vision Abnormal	2%	1
	Conjunctivitis/Eye Pain	1%	1
	Tinnitus	1%	0.
PSYCHIATRIC:	Somnolence	5%	
	Nervousness	2%	
	Depression	1%	
	Insomnia	1%	
	Sexual Dysfunction	2%	
GASTROINTESTINAL:	Nausea	3%	
	Diarrhea	2%	
	Constipation	1%	1
	Dyspepsia	1%	1
	Flatulence	1%	1
	Abdominal Pain	0%	
	Vomiting	0%	1
RESPIRATORY:	Rhinitis	3%	1
	Dyspnea	1%	1
	Epistaxis	1%	
URINARY:	Polyuria	2%	
	Urinary Incontinence	1%	
	Micturation Frequency	0%	
GENERAL:	Fatigue/Malaise	12%	
	Chest Pain	2%	
	Asthenia	1%	1
	Face Edema	1%	
	Pain	2%	

Additional adverse reactions have been reported, but these are, in gene not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-ter clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonom Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoieti* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatr* paroniria, amnesia, emotional lability, abnormal thinking, depersonalizati *Special Senses:* parosmia, earache, taste perversion, photophobia, abnorn lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* flushes, back pain, infection, fever/rigors, decreased weight, influenza-lik symptoms.

CARDURA has not been associated with any clinically significant chang in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitroge creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dos syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dos and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increas to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve t desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 m (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 m (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 19

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References: 1. The Treatment of Mild Hypertension Research Group. Treatment of Mild Hypertension Study: a randomized, placebo-controlled of a nutritional-hygienic regimen along with various drug monotherap *Arch Intern Med.* 1991;151:1413-1423. **2.** Lehtonen A, the Finnish Multice Study Group. Lowered levels of serum insulin, glucose, and cholester hypertensive patients during treatment with doxazosin. *Curr Ther* 1990;47:278-284.

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Comparison of Thrombolytic Therapy for Acute Myocardial Infarction in Patients Aged <35 and >55 Years

Lalit Chouhan, Hajar A. Hajar, and Juan Carlos Pomposiello

Sixty-two patients aged <35 years and 58 the aged >55 years who received intravenous streptokinase for acute myocardial infarction were studied. Younger patients had a higher incidence of smoking and a lower incidence of diabetes mellitus. At angiography, younger patients had a higher incidence of insignificant coronary artery disease and a lower incidence of 3-vessel disease than did older ones. The patency rates of the infarct vessel were comparable in both age groups. Long-term follow-up is needed to examine differences in prognosis due to differences in risk factor profile and coronary anatomy.

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Relation of Apolipoprotein E Phenotype to Myocardial Infarction and Mortality from Coronary Artery Disease

June E. Eichner, Lewis H. Kuller, Trevor J. Orchard, Gregory A. Grandits, Lisa M. McCallum, Robert E. Ferrell, and James D. Neaton

The role of apolipoprotein E phenotype as a risk factor for coronary artery disease (CAD) is examined using 619 of the 12,866 randomized participants from the Multiple Risk Factor Intervention Trial. Study subjects representing 93 CAD deaths and 113 nonfatal myocardial infarctions were matched with 412 control subjects in a nested patient-control design. Serum frozen at –60 to –70°C for about 15 years was used for phenotyping apolipoprotein E. A significant difference in low-density lipoprotein cholesterol was found between phenotypes ($p < 0.001$) with the apolipoprotein E 3-2 group having a 20 to 25 mg/dl lower mean LDL cholesterol than the other phenotype groups. The distribution of apolipoprotein E phenotype differed between patient and control subjects with the patients having a higher percentage of apolipoprotein E phenotypes 4-3, 4-4 and 4-2 and a smaller percentage of apolipoprotein E 3-3 than control subjects. This effect was stronger in the CAD deaths.

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Value of Rest Thallium-201/Technetium-99m Sestamibi Scans and Dobutamine Echocardiography for Detecting Myocardial Viability

Paolo Marzullo, Oberdan Parodi, Barbara Reisenhofer, Gianmario Sambuceti, Eugenio Picano, Alessandro Distante, Alessia Gimelli, and Antonio L'Abbate

To define the relation between myocardial viability, rest thallium-201 and technetium-99m sestamibi uptakes and dobutamine echocardiography, 14 patients with ventricular dysfunction were studied with different approaches. Each patient underwent, on separate days, rest early (10-minute) and delayed (16-hour) thallium-201 scan, rest sestamibi scintigraphy, dobutamine echocar-

diography and coronary angiography. Before revascularization, 75 segments were dyssynergic on echocardiography. Recovery of regional function after coronary recanalization was used as the gold standard for viable myocardium. Delayed thallium-201 activity and echocardiographic response to dobutamine showed good sensitivity and specificity in the preoperative characterization of viable myocardium; early thallium-201 scan and sestamibi showed the highest rate of false-positive and false-negative results.

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Unrecognized Left Main Coronary Artery Disease in Patients Undergoing Interventional Procedures

James B. Hermiller, Christopher E. Buller, Alan N. Tenaglia, Katherine B. Kisslo, Harry R. Phillips, Thomas M. Bashore, Richard S. Stack, and Charles J. Davidson

Selective, coronary arteriographic, mechanically driven, catheter-based, intravascular ultrasound images were obtained to determine the presence and extent of angiographically undetected or underestimated left main (LM) coronary arterial narrowing in 38 patients undergoing coronary interventional therapy. Abnormal coronary arteriograms were digitized and quantitated using a semiautomated edge-detection algorithm. Intravascular ultrasound detected plaque in 24 of 27 angiographically normal LM arteries (89%), whereas narrowing was observed in 11 of 11 angiographically abnormal LM arteries (100%). Eight of thirty-eight patients (21%) had >40% area stenosis by intravascular ultrasound. In patients with angiographic disease, there was no correlation between quantitative angiographic and ultrasound percent area stenosis ($r = 0.12$; $p = 0.72$; SEE 19%). The median plaque area was not different between angiographically normal (0.05 cm^2; 0.03, 0.08 [25th, 75th percentile]) and abnormal (0.06 cm^2; 0.03, 0.1) patients. The median percent area stenosis in arteriographically normal subjects (26%; 14, 32%) was less than that in abnormal ones (37%; 20, 46%) ($p = 0.03$). Unrecognized LM disease is widespread and often underestimated in patients with normal LM angiograms undergoing interventional procedures. Plaque area is similar for angiographically normal and insignificantly abnormal vessels. Intravascular ultrasound appears to overcome the limitations of silhouette imaging and can be a clinically useful, adjunctive method to evaluate LM coronary artery disease.

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Transient Myocardial Ischemia During Nifedipine Therapy in Stable Angina Pectoris, and Its Relation to Coronary Collateral Flow and Comparison with Metoprolol

Kenneth Egstrup and Poul Erik Andersen, Jr.

The anti-ischemic effect of nifedipine and metoprolol on ambulatory electrocardiographic ischemia was studied in 41 patients with stable angina and proven coronary artery disease, and was related to the presence of coronary collateral flow. Seventeen patients had angiographically poor or no collateral flow (group 1), and 24 had good collateral flow (group 2). Nifedipine reduced ambulatory ischemic activity in 8 patients with no collateral flow ($p < 0.05$), whereas increases in both total ($p < 0.05$) and silent ($p < 0.01$) ischemia were observed in 12 with good collateral flow. Reflex tachycardia

Continued on page A18

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1. Naschitz JE, Yeshurun D, Odeh M, et al. Overt gastrointestinal bleeding in the course of chronic low-dose aspirin administration for secondary prevention of arterial occlusive disease. *Am J Gastroenterol.* 1990; 85(4):408-410.
2. Faigel DJ, Jakubowski JA, Stampfer MJ, et al. Multiple doses of regular and enteric-coated aspirin produce equivalent platelet inhibitory effects. *Curr Ther Res.* 1986; 39(4):519-527.

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was not observed at the onset of ischemia. Metoprolol reduced both total (p <0.01) and silent (p <0.01) ischemia independent of coronary collateral flow. The findings indicate a relation between coronary collateral flow and the anti-ischemic effect of nifedipine that may explain the conflicting results in patients with chronic stable angina. Increased ischemic activity during nifedipine therapy may be due to a coronary steal phenomenon.

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Comparison of Two Mechanical Ultrasound Devices With and Without Echogenic Contrast Dye

Karl M. Schmid, Jürgen Mewald, Wolfram Voelker, Hans-Jörg Paul, Manfred Wehrmann, Burkhart Bültmann, and Karl R. Karsch

To evaluate the impact and limitations of intracoronary ultrasound, 64 segments of 13 isolated coronary arteries were examined comparing 2 mechanical devices (device A, 30 MHz 5Fr [CVIS]; device B, 20 MHz 4.8Fr [Diasonics/Boston Scientific]) with the corresponding histologic specimens. After application of contrast dye (Laevovist®, Schering AG, Germany), correlation of luminal area between histology and ultrasound improved from $r = 0.62$ to $r = 0.77$ (device B, $p < 0.05$) and from $r = 0.82$ to $r = 0.88$ (device A; p = NS). Low accuracy of lumen measurements in segments <2.5 mm could be improved by application of contrast dye. For the assessment of wall thickness only in segments >2.5 mm, a reliable correlation between ultrasound and histology was found (device A, $r = 0.80$; device B, $r = 0.60$). Sensitivity of plaque ($n = 51$) detection was lower for device B (63%) than for device A (82%, $p < 0.05$), and measurements correlated with histology only for device A. There are considerable differences in the accuracy of ultrasound measurements between mechanical systems. Nevertheless, additional application of contrast dye can improve accuracy of luminal measurements.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Left Atrial Appendage Flow Velocity Assessment Using Transesophageal Echocardiography in Nonrheumatic Atrial Fibrillation and Systemic Embolism

Patrick M. J. Verhorst, Otto Kamp, Cees A. Visser, and Freek W. A. Verheugt

Transesophageal echocardiography was performed in 54 patients with nonrheumatic atrial fibrillation (16 patients with and 38 without documented systemic embolism), evaluating the presence of left atrial (LA) appendage thrombus, LA spontaneous contrast, LA size, systolic and diastolic peak velocity of the left pulmonary vein, and forward and backward peak velocity of the LA appendage. No difference was noted in LA appendage thrombus, LA size, or peak flow velocities of the left pulmonary vein between the 2 groups. In the group with embolism, significantly more patients had LA spontaneous contrast ($p = 0.01$) and lower peak flow velocities of the LA appendage ($p < 0.05$). Measurement of LA appendage flow velocity using

Continued on page A21

The largest U.S. double-blind, placebo-controlled trial of patients with moderate hypercholesterolemia

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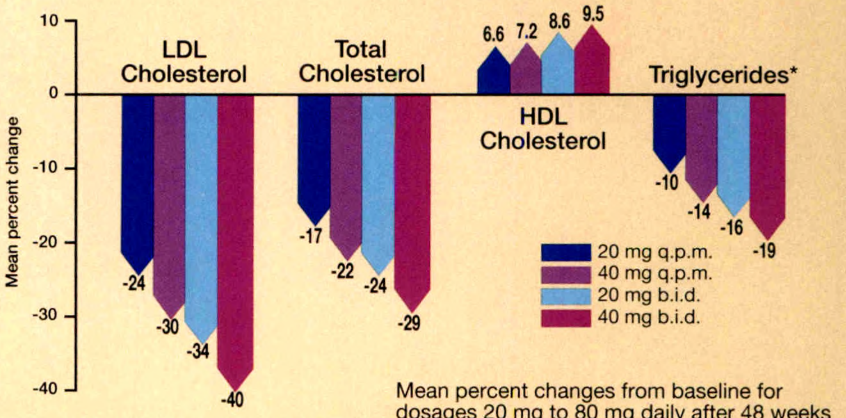

Mean percent changes from baseline for dosages 20 mg to 80 mg daily after 48 weeks of treatment (n=6,582)

* Triglyceride values are expressed as median changes.

1. Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, Arch. Intern. Med. *151*:43-49, January 1991.

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For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR®*
(LOVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS)

Pregnancy and lactation

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses ($\geq$1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in $\geq$1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m (n=1,642) %	40 mg q.p.m (n=1,645) %	20 mg b.i.d (n=1,646) %	40 mg b.i.d (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m^2

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.
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transesophageal echocardiography may potentially identify patients with nonrheumatic atrial fibrillation at high risk for embolism.

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Comparison of Biphasic and Monophasic Shocks for Defibrillation Using a Nonthoracotomy System

D. George Wyse, Katherine M. Kavanagh, Anne M. Gillis, L. Brent Mitchell, Henry J. Duff, Robert S. Sheldon, Teresa M. Kieser, Andrew Maitland, Patricia Flanagan, John Rothschild, and Rahul Mehra

Biphasic shocks for defibrillation using a nonthoracotomy system had a lower ($p < 0.001$) defibrillation threshold (stored energy) than did monophasic shocks in patients having a defibrillator implanted (12.3 ± 5.3 vs 21.1 ± 9.3 J) who were studied with their chests closed and in those undergoing coronary artery bypass grafting (14.6 ± 7.1 vs 24.2 ± 12.6 J) who were studied with their chests open but reapproximated. These values are less than were previously reported using a similar nonthoracotomy lead configuration. There were important clinical differences between the 2 groups of subjects, but no differences in measurements of defibrillation. It is concluded that patients undergoing coronary artery bypass grafting may be a potential source of surrogate subjects for defibrillation research that requires the chest to be opened.

CONGESTIVE HEART FAILURE

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Effects of Intravenous Milrinone on Left Ventricular Function in Ischemic and Idiopathic Dilated Cardiomyopathy

Stephen J. D. Brecker, Han B. Xiao, Mouanodji Mbaissouroum, and Derek G. Gibson

The effects of intravenous phosphodiesterase inhibition on ventricular function in ischemic and idiopathic dilated cardiomyopathy were studied in 12 patients with echocardiography and Doppler. Cardiac index increased, without change in heart rate or blood pressure. Longitudinal mitral ring motion, which had been uniformly reduced, increased markedly after milrinone. Left ventricular cavity size decreased, and shortening fraction, posterior wall thickness, and rates of posterior wall thickening and thinning increased markedly. Left atrial pressure decreased, and isovolumic relaxation time increased. However, the peak velocity and duration of the transmitral E wave increased. Improved longitudinal (subendocardial) function was thus reflected by improved posterior wall dynamics, and early filling. Severely reduced subendocardial function in dilated cardiomyopathy is reversible, with marked effects on systolic and diastolic function. These previously unrecognized actions of milrinone provide further evidence to justify its short-term use in supporting the severely depressed myocardium.

Continued on page A24

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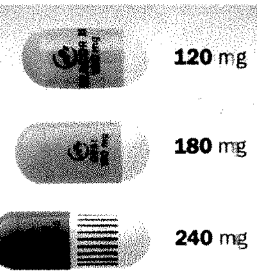

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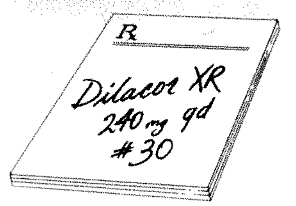

BRIEF SUMMARY

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant ß-adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with the histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Dilacor™ XR utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Dilacor™ XR.

Information for Patients. Dilacor™ XR capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor™ XR capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor™ XR. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The most common adverse events (frequency ≥1%) in placebo-controlled, clinical hypertension studies with Dilacor™ XR using daily doses up to 540 mg are listed in the table below with placebo-treated patients included for comparison.

MOST COMMON ADVERSE EVENTS
IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRIALS*

Adverse Events (COSTART Term)	Dilacor™ XR n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving Dilacor™ XR.

The following additional events (COSTART Terms), listed by body system, were reported infrequently in all subjects and hypertensive patients who received Dilacor™ XR (n=425): Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation; Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence; Digestive System: Dry mouth, anorexia, tooth disorder, eructation; Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus); Respiratory System: Epistaxis, bronchitis, respiratory disorder; Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease; Metabolic and Nutritional Disorders: Gout, edema; Musculoskeletal System: Arthralgia, bursitis, bone pain; Hemic and Lymphatic Systems: Lymphadenopathy; Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses: Amblyopia (blurred vision), ear pain.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine or dobutamine) and diuretics.

Hypotension: Vasopressors (*e.g.* dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluating cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Please see product circular for full prescribing information.

References:

1. Graney WF: Clinical experience with a once-daily, extended-release formulation of diltiazem in the treatment of hypertension. *Am J Med* 1992;93(Suppl 2A): 565-645.
2. *1992 Drug Topics® Red Book® Update.* Oradell, NJ, Medical Economics Co. Inc.; December 1992.

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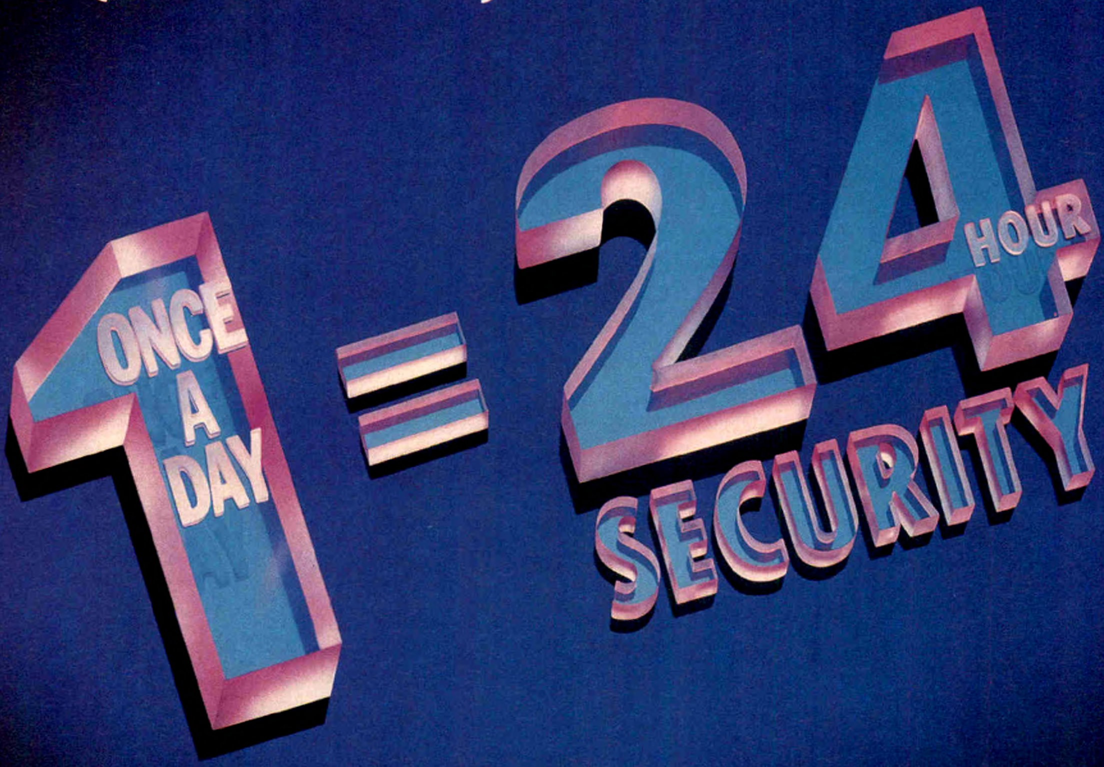

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VALVULAR HEART DISEASE

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Comparison of Transthoracic and Transesophageal Echocardiography for Detection of Abnormalities of Prosthetic and Bioprosthetic Valves in the Mitral and Aortic Positions

Werner G. Daniel, Andreas Mügge, Jochen Grote, Dirk Hausmann, Peter Nikutta,
Joachim Laas, Paul R. Lichtlen, and Randolph P. Martin

One hundred twenty-six patients with 148 prosthetic valves were studied by both transesophageal (TEE) and transthoracic (TTE) M-mode and 2-dimensional echocardiography. Prosthetic valve morphology was confirmed by surgery or autopsy in all cases; 124 prostheses were classified as diseased and 24 normal. Prosthetic valve endocarditis and thrombi were correctly identified by TTE in 36 and 13% of cases, respectively, but could be diagnosed by TEE in 82% ($p < 0.001$) and 100% ($p < 0.01$), respectively. Overall, sensitivity and specificity were 57 and 63%, respectively, for TTE, and 86 and 88%, respectively, for TEE. TEE is superior to TTE in the correct identification of morphologic prosthetic valve abnormalities, and should therefore be used in patients with suspected prosthetic valve malfunction and negative TTE.

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Color Doppler Echocardiographic Determination of Mitral Regurgitant Flow from the Proximal Velocity Profile of the Flow Convergence Region

Martin Giesler, Georg Grossmann, Arnold Schmidt, Matthias Kochs, Joachim
Langhans, Martin Stauch, and Vinzenz Hombach

A new method for determination of mitral regurgitant flow rate from color Doppler echocardiographic maps of the flow convergence region was prospectively evaluated. The proximal velocity profile along the flow center line of the flow convergence region was measured by color Doppler echocardiography. Regurgitant flow rate was determined by comparing the resulting curve to reference curves that were derived from in vitro measurements and contained in a nomogram. In 74 patients (19 without and 55 with angiographic mitral regurgitation), regurgitant flow rate ranged from 0 to 600 ml/s and correlated closely with angiographic grade. Using additional continuous-wave Doppler, regurgitant stroke volume was calculated as regurgitant flow rate • velocity-time integral/regurgitant maximum velocity. In 16 patients, regurgitant stroke volume correlated significantly ($r = 0.88$) with invasive measurements (angiography/Fick method) with a regression line close to identity ($y = 0.89x + 12.7$ ml). The proximal velocity profile method enables assessment of mitral regurgitation with estimation of absolute regurgitant volumes.

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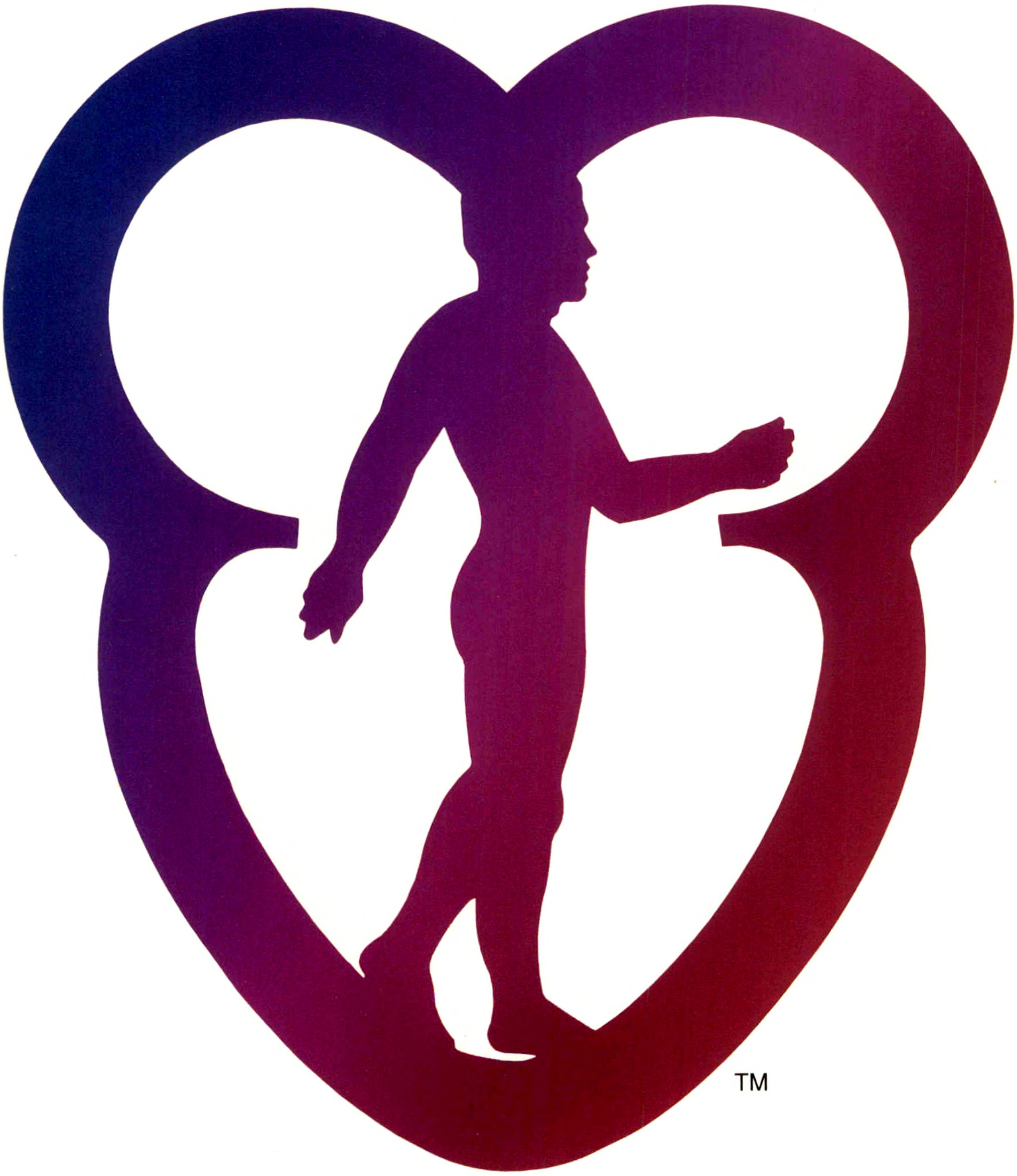

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Cineradiography for Determination of Normal and Abnormal Function in Mechanical Heart Valves

Werner Vogel, Hans Peter Stoll, Wolfgang Bay, Gerd Fröhlig, and Hermann Schieffer

Cineangiography was performed in 95 mechanical heart valves of different types in order to examine structural integrity and parameters of valve motion in patients with symptoms of potentially valve-related complications and in asymptomatic control subjects. Incomplete or asymmetric disk opening suggestive of thrombosis or tissue ingrowth was significantly more pronounced in patients than in control subjects. Differences were not significant for valve opening and closing times. Structural failure can equally be recognized early if x-ray projections are adapted to the specific valve design. The method is of high value for routine and emergency cases and may help to identify patients at risk of acute valve malfunction.

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Balloon Mitral Commissurotomy in Patients Aged ≥70 Years

Claude Le Feuvre, Raoul Bonan, Marie-Laure Lachurie, Yves Leclerc, Robert Petitclerc, Ihor Dyrda, and Jacques Crépeau

Among 280 consecutive patients with balloon mitral commissurotomy performed from 1987 to 1991, 28 were ≥70 years old. Two patients with associated significant aortic stenosis were excluded from this study. Acute complications during the procedure and 30-day mortality occurred in 8 and 5 patients, respectively. A complete hemodynamic success was obtained in 16 patients (72%). Mitral valve area ($p < 0.01$) and total pulmonary resistance ($p < 0.01$) were independent predictors of success. At 6 months, 20 patients had improvements of ≥1 functional class, and 13 remained improved after a mean follow-up of 28 ± 17 months. Patients with a long-term functional improvement had a lower baseline echocardiographic score than did the remaining ones (7.8 ± 2.0 vs 10.6 ± 1.7; $p < 0.01$). The survival rate at 3 years was 70%.

MISCELLANEOUS

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Effects of Successful Cardiac Transplantation on Plasma Endothelin

Garrie J. Haas, Margaret Wooding-Scott, Philip F. Binkley, P. David Myerowitz, Robert Kelley, and Robert J. Cody

After cardiac transplantation, cyclosporine-treated patients have a high incidence of systemic hypertension, the mechanism of which is not known. Endothelin, a potent vasoconstrictor peptide of endothelial origin, may be activated by cyclosporine-induced endothelial injury and therefore may mediate post-transplant hypertension. This study tested whether endothelin-1 could be detected in the plasma of cardiac transplant patients and whether levels correlated with hemodynamic characteristics, serum creatinine or cyclosporine levels. Twenty-two cyclosporine-treated cardiac transplant pa-

tients were studied at the time of routine heart biopsy. Plasma endothelin-1 was significantly elevated (5.2 ± 1.8 pg/ml) compared with 12 normal subjects (1.9 ± 0.3 pg/ml). Heart rate, systemic and pulmonary pressures and resistances, and serum creatinine were significantly increased in the transplant group. Cardiac index was normal. Endothelin did not correlate with any hemodynamic variable, serum creatinine or cyclosporine level. Thus, endothelin-1 is increased after cardiac transplantation. In the absence of discrete correlations with hemodynamic variables, serum creatinine or cyclosporine level, both the characteristics and mechanisms for increased endothelin in cardiac transplant recipients requires further evaluation.

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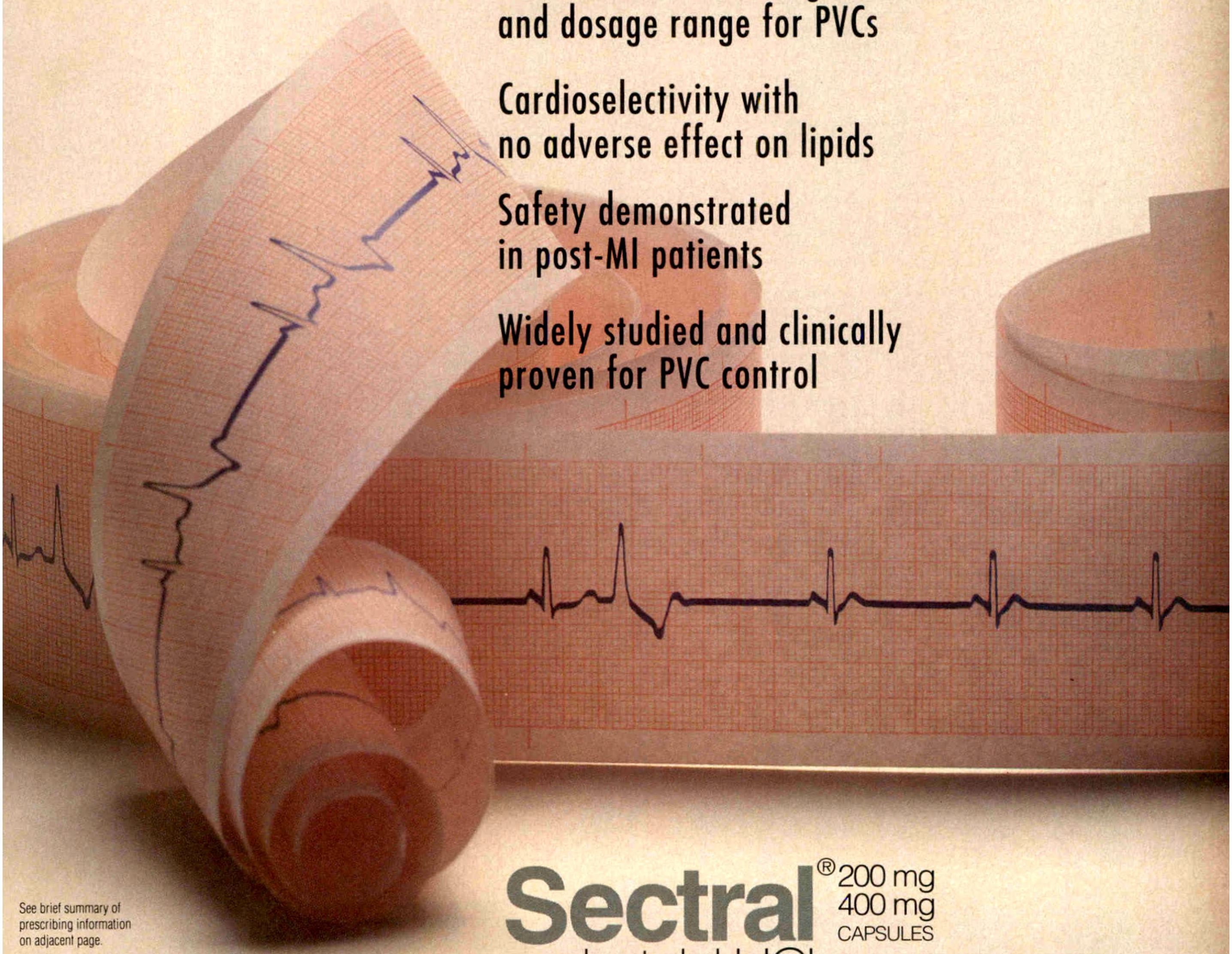

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(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N =1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuro-psychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

3482-5 6/21/89

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READERS' COMMENTS

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CLASSIFIED ADVERTISING on pages A66, A67, A68, A69, A70 and 3rd Cover

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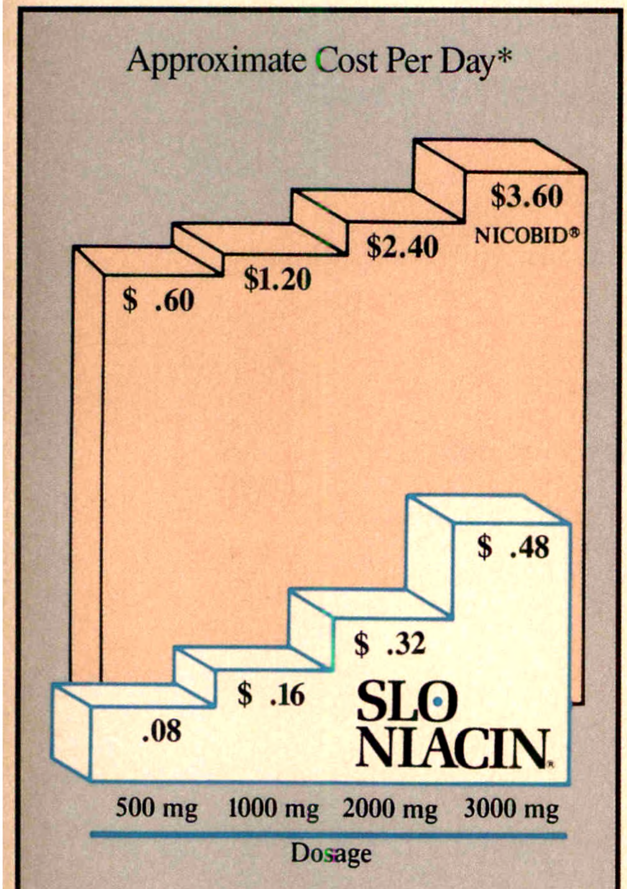

*Based on AWP, *Redbook* Oct., 1990.

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C.J. Lavie, et al.: *Postgraduate Medicine*, May 15, 1990.

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JANUARY 15, 1993, VOL. 71, NO. 2

Impact of Treatment Strategy on Predischarge Exercise Test in the Thrombolysis in Myocardial Infarction (TIMI) II Trial

Bernard R. Chaitman, MD, Robert P. McMahon, PhD, Michael Terrin, MD,
Liwa T. Younis, MD, PhD, Leslee J. Shaw, MA, Donald A. Weiner, MD,
Margaret M. Frederick, PhD, Genell L. Knatterud, PhD, George Sopko, MD,
and Eugene Braunwald, MD, for the TIMI Investigators*

Predischarge supine bicycle ergometry was used to assess persistent myocardial ischemia in postinfarction patients who received thrombolytic therapy and were randomized to an invasive versus conservative strategy in the Thrombolysis in Myocardial Infarction (TIMI) II trial. The frequency of ischemic responses in both strategies, and the 1-year prognostic importance of the different exercise test outcomes were examined. At 14 days, the percentage of patients with any adverse outcome (including death, presence of exercise-induced ST-segment depression, or inability to perform the exercise test) was 33.7% of 1,681 randomly assigned to the invasive strategy compared with 34.6% of 1,658 randomly assigned to the conservative strategy (p = 0.57). The 1-year mortality was greater in patients who did not perform the predischarge exercise test (7.7%) than in those who did (1.8%) (p <0.001); the former were older, and a greater proportion were women, had a more frequent history of myocardial infarction, and more extensive coronary artery disease (p <0.01 for each comparison). The 1-year mortality in patients with exercise-induced ST-segment depression or chest pain was only 1.4% (3 of 222) among those randomly assigned to the conservative strategy where coronary angiography and revascularization were recommended if the test result was abnormal (relative risk compared with those without ST-segment depression or chest pain 0.6; 99% confidence interval 0.1 to 2.9). Among patients randomly assigned to the invasive strategy, exercise-induced ST-segment depression or chest pain was associated with a 1-year mortality of 2.5% (4 of 161) (relative risk compared with those without ST-segment depression or chest pain 2.1; 99% confidence interval 0.5 to 9.4). Thus, in postinfarct patients treated with thrombolytic therapy and a conservative strategy, the recommendation of performing cardiac catheterization and coronary revascularization when the predischarge exercise test is abnormal results in a low 1-year mortality for those with exercise-induced angina or ST-segment depression, which is comparable to that for patients who do not have these findings.

(Am J Cardiol 1993;71:131-138)

The Thrombolysis in Myocardial Infarction (TIMI) II trial assessed the role of cardiac catheterization 18 to 48 hours after study entry, with percutaneous transluminal coronary angioplasty (PTCA) if appropriate, in patients with acute myocardial infarction treated with recombinant tissue-type plasminogen activator. The principal goal of TIMI II was to determine if this invasive treatment strategy would alter mortality and reinfarction as compared with a conservative strategy. There were no significant differences in the occurrence of death or reinfarction between treatment strategies at 6 weeks or 1 year after enrollment.[1-3]

Predischarge submaximal exercise testing is frequently performed after an acute myocardial infarction to determine prognosis, functional capacity and propensity to develop cardiac arrhythmias, and to provide a baseline for exercise prescription in the convalescent phase.[4-18] Evaluation of postinfarction exercise testing as a procedure for risk stratification should consider the impact of the referral for coronary angiography in patients with an abnormal test, and subsequent coronary

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From the Maryland Medical Research Institute, Baltimore, Maryland. Dr. Chaitman's current address is: St. Louis University Medical Center, 3635 Vista Avenue at Grand Boulevard, P.O. Box 15250, St. Louis, Missouri 63110-0250. This study was supported by research contracts and grants from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received May 7, 1992; revised manuscript received August 28, 1992, and accepted August 31.

Address for reprints: TIMI Coordinating Center, Maryland Medical Research Institute, Inc., 600 Wyndhurst Avenue, Baltimore, Maryland 21210.

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*Investigators and participating centers are published in the *New England Journal of Medicine* (1989:320;618–627).

revascularization.[19] In some patients, the revascularization procedure may influence the natural history of the disease and alter the prognosis associated with abnormalities observed during exercise testing. A second consideration is the use of thrombolytic therapy, a treatment known to decrease mortality, now received by 20 to 40% of patients who present to the hospital with suspected infarction.[20,21] There is little information regarding the prognostic role of predischarge exercise testing in patients with myocardial infarction treated with a thrombolytic agent. In this report, we present the frequency of electrocardiographic evidence of exercise-induced ischemia at hospital discharge, document the use of the exercise test to select patients enrolled in the conservative strategy for cardiac catheterization, and compare the prognosis of patients with and without selected exercise test abnormalities in the invasive and conservative strategies. The predischarge exercise test included the use of radionuclide ventriculography, the results of which were reported previously.[22]

METHODS

Study patients: The details of the TIMI II trial and inclusion/exclusion criteria have been described.[1–3] Patients were eligible for enrollment if they had chest discomfort suggestive of acute myocardial ischemia lasting ≥30 minutes, and ST-segment elevation ≥0.1 mV in electrically contiguous leads, were aged <76 and had no contraindications to receiving a thrombolytic drug. Patients were enrolled within 4 hours of the onset of symptoms that precipitated hospital admission. The TIMI II protocol was approved by the human research committee at each participating medical center, and written informed consent was obtained from all patients.

In all, 3,339 patients were enrolled; 1,681 were randomly assigned to an invasive strategy of PTCA to the infarction-related artery when the coronary anatomy was suitable 18 to 48 hours after treatment, and 1,658 were randomly assigned to a conservative strategy in which they were evaluated for revascularization if they had spontaneous ischemia after infarction during the hospital phase, or important exercise-induced myocardial ischemia during an exercise test performed before hospital discharge. Of 3,339 patients in the trial, 2,502 (75%) performed exercise testing within 2 weeks of the index event (Figure 1). Exercise electrocardiograms were considered noninterpretable for the development of ischemia in 147 patients, because of electrocardiographic findings of left ventricular hypertrophy, bundle branch block or excess motion artifact during exercise. This analysis is based on the remaining 2,355 patients with exercise electrocardiograms analyzed at the TIMI Electrocardiographic Core Laboratory (1,168 patients randomly assigned to the invasive strategy and 1,187 to the conservative strategy). Baseline characteristics of the patients who did perform versus those who did not perform the exercise test in the invasive and conservative strategies are listed in Table I. Of 960 patients in whom medication usage at the time of exercise testing was recorded, 66% received β-blocker drugs, 48% calcium antagonist, 26% long-acting nitrates and 5% digoxin within 7 days of testing.

Exercise protocol: Exercise was performed in the supine position using a calibrated electronic bicycle ergometer. Heart rate, systemic blood pressure measured by sphygmomanometry, and a 12-lead electrocardiogram were recorded at baseline, the end of each exercise stage, peak exercise and each minute for 5 minutes into the recovery phase. The initial work load of the 2-stage exercise test was set at 200 kpm and increased to 400 kpm after 3 minutes or to a peak heart rate of 120 beats/min for patients during the limited, predischarge

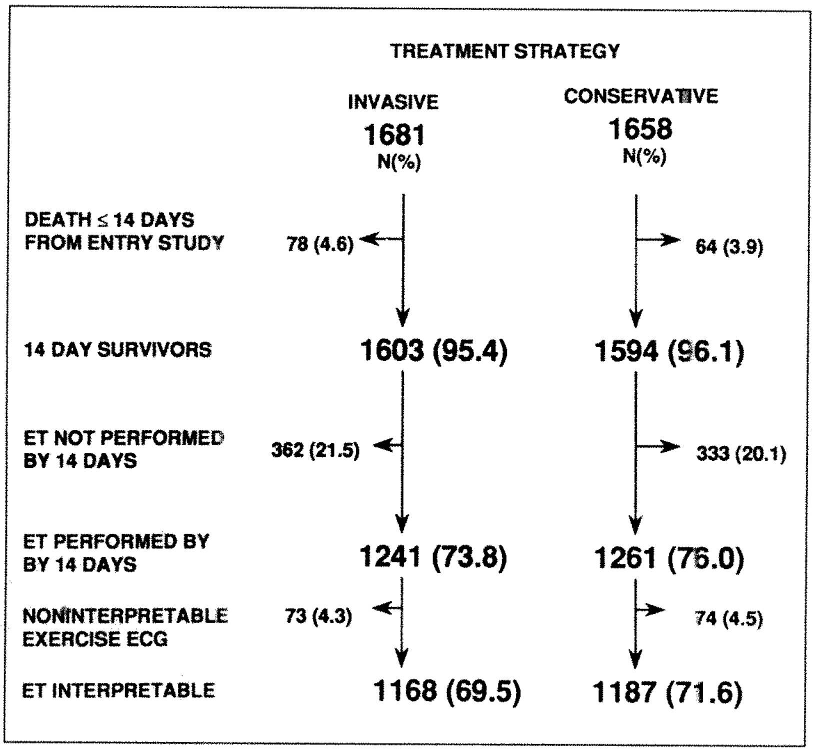

FIGURE 1. Performance of exercise test (ET), and availability of exercise electrocardiographic data. There were 1,681 and 1,658 patients in TIMI II randomized to invasive and conservative strategies, respectively. ECG = electrocardiogram.

TABLE I Patient Characteristics According to Treatment Strategy and Whether Patients Performed an Exercise Test ≤ 14 Days After Study Entry*

	Invasive			Conservative		
Baseline Characteristics	Exercise Test (n = 1,241); n (%)	No Exercise Test (n = 362); n (%)	p Value†	Exercise Test (n = 1,261); n (%)	No Exercise Test (n = 333); n (%)	p Value†
Mean age (year)	55.6	59.5	0.001	55.8	59.1	0.001
Race (white)	1,088 (87.7)	320 (88.4)	0.71	1,127 (89.4)	288 (86.5)	0.14
Sex (men)	1,059 (85.3)	270 (74.6)	0.001	1,066 (84.5)	251 (75.4)	0.001
Not low risk‡	781 (62.9)	258 (71.3)	0.003	826 (65.5)	236 (70.9)	0.06
Age ≥ 70 years	118 (9.5)	68 (18.8)	0.001	101 (8)	59 (17.7)	0.001
Prior myocardial infarction	154 (12.4)	68 (18.8)	0.002	155 (12.3)	59 (17.7)	0.01
Anterior myocardial infarction	604 (48.7)	192 (53)	0.14	662 (52.5)	175 (52.6)	0.99
Rales ≥ 1/3 of lung fields	35 (2.8)	19 (5.2)	0.02	43 (3.4)	16 (4.8)	0.23
Hypotension and sinus tachycardia	63 (5.1)	18 (5)	0.94	64 (5.1)	19 (5.7)	0.64
Atrial fibrillation or flutter	23 (1.8)	8 (2.2)	0.66	25 (2)	10 (3)	0.26
Pulmonary edema	7 (0.6)	7 (1.9)	0.01	8 (0.6)	6 (1.8)	0.04
Cardiogenic shock	12 (1)	6 (1.7)	0.27	10 (0.8)	4 (1.2)	0.48
History						
Angina	652 (52.5)	221 (61.2)	0.004	651 (51.6)	189 (56.8)	0.10
Congestive heart failure	25 (2)	22 (6.1)	0.001	24 (1.9)	12 (3.6)	0.06
Hypertension	453 (36.5)	165 (45.6)	0.002	461 (36.6)	132 (39.6)	0.30
Diabetes	130 (10.5)	61 (16.8)	0.001	158 (12.5)	51 (15.3)	0.18
Current smoker	632 (50.9)	159 (43.9)	0.02	657 (52.1)	142 (42.6)	0.002
Ever smoked	961 (77.4)	270 (74.6)	0.26	1,000 (79.3)	247 (74.2)	0.04
Time from onset to study entry ≤2 hours	323 (26)	101 (27.9)	0.48	317 (25.1)	94 (28.2)	0.25
Cardiovascular events ≤ 14 days						
Myocardial infarction	46 (3.7)	44 (12.2)	0.001	40 (3.2)	33 (9.9)	0.001
Recurrent painful ischemic events in hospital	254 (20.5)	133 (36.7)	0.001	304 (24.1)	155 (46.5)	0.001
New congestive heart failure	161 (13)	102 (28.2)	0.001	155 (12.3)	90 (27.1)	0.001
Any of above	371 (29.9)	190 (52.5)	0.001	414 (32.8)	197 (59.2)	0.001
CABG	38 (3.1)	126 (34.8)	0.001	36 (2.9)	69 (20.7)	0.001

*Analysis is restricted to 14-day survivors.

†p value for difference between patients who did and did not exercise by 14 days within each treatment strategy.

‡Patient is not low risk if any of following are present on admission: age ≥ 70 years, prior myocardial infarction, anterior myocardial infarction, rales ≥ 1/3 of lung fields, hypotension and sinus tachycardia, atrial fibrillation or flutter, pulmonary edema, or cardiogenic shock.

CABG = coronary artery bypass grafting.

exercise test. The maximal duration of the test was 6 minutes. The limited, predischarge exercise test was discontinued for the development of progressive chest pain, excessive dyspnea, dizziness, complex ventricular arrhythmias, exertional hypotension, severe ischemic ST-segment depression, excessive fatigue, or achievement of target heart rate or work load.

At the Electrocardiographic Core Laboratory, each 12-lead electrocardiogram obtained before exercise, at peak exercise and during recovery was reviewed for ST-segment shifts ≥0.05 mV. When ST-segment deviation was ≥0.05 mV, the electrocardiographic leads with the most marked ST-segment depression and elevation were digitized, using a SummaGraphics microgrid II digitizer interfaced to an IBM computer. Three consecutive complexes were digitized at rest and peak exercise, and in the recovery phase if ST-segment deviation exceeded that observed at peak exercise or immediately after exercise. Custom software was used to analyze the rest and maximal ST-segment changes observed during peak exercise or in recovery.[23,24] The exercise electrocardiographic response was considered abnormal when either of the following 2 criteria were observed in any lead as compared with at baseline: J point and ST-80 depression ≥0.1 mV, ST-segment slope <1 mV/s; or J point and ST-80 depression ≥0.15 mV, and ST-segment slope >1 mV/s. ST-segment elevation in Q-wave infarct leads was determined to be present when J point and ST-80 elevation was >0.1 mV as compared with at baseline and was not considered an ischemic response.

At the time of the hospital discharge study, results were interpreted locally by clinical center staff to determine if evidence of exercise-induced myocardial ischemia was present. For conservative strategy patients, the TIMI II protocol indicated coronary angiography (to be followed by revascularization if necessary) when spontaneous or exercise-induced myocardial ischemia was present. Otherwise, cardiac catheterization was discouraged. Indicators of myocardial ischemia considered in the evaluation for coronary angiography included angina pectoris, ST-segment depression ≥2 mm, a 20 mm Hg reduction in systolic blood pressure, a 5-unit reduction in left ventricular ejection fraction, and complex ventricular arrhythmias. The test outcome was considered inconclusive when the aforementioned indicators were absent, and if patients were unable to exercise to a heart rate of 120 beats/minute or could not perform at a work load of 400 kpm.

End points: The TIMI II protocol required that all patients complete a 6-week and 1-year clinic visit. All deaths and nonfatal events that occurred during follow-up were reported to the Coordinating Center. Information was collected from all surviving patients for cardiac events including reinfarction, congestive heart failure, presence of angina pectoris and whether a revascularization procedure had been performed. As of January 1991, 1-year follow-up for vital status was 99% complete for both treatment strategies. Reinfarction was classified centrally without knowledge of treatment assignment and accepted as documented according to previously published criteria.[2]

Statistical analysis: To account for all patients who entered the study, a composite 14-day adverse outcome was defined by death within 14 days of study entry, survival to 14 days without a hospital discharge exercise test, or a hospital discharge exercise electrocardiogram with ischemic ST depression present.

Analysis of exercise test findings as predictors of events (death, death or myocardial infarction by 1 year after study entry) was restricted to patients alive at 14 days who performed the exercise test and whose exercise electrocardiogram was analyzed at the Electrocardiographic Core Laboratory. The proportions of patients experiencing events were estimated by the Kaplan-Meier method[25]; comparisons of survival without events were performed by the log-rank test.[26] The relative risk reported for each exercise finding estimates the ratio of the risk of events for patients with the finding present to that for those without the finding. The Cox proportional hazards model[27] was used to estimate relative risks and confidence intervals. For comparison of baseline variables, chi-square tests were used to compare categoric variables and *t* tests for continuous variables. To account for the multiple statistical hypotheses tested, $p < 0.01$ was considered to show evidence of a relation, and $p < 0.001$ strong evidence. All data analyses were conducted with the SAS or BMDP statistical packages.[28,29] The analyses were performed on an analysis file created at the Coordinating Center in January 1991.

RESULTS

At 14 days after entry in the TIMI II trial, the proportion of patients who died, had not performed the exercise test or had exercise-induced ST-segment depression were similar in the invasive and conservative strategies (Figure 2; $p = 0.57$). The proportion of patients who died, had a new myocardial infarction, had not performed the exercise test or had exercise-induced ST-segment depression were similar in the invasive and conservative strategies (36.0 vs 36.7%; $p = 0.69$).

Patients who did not perform a predischarge exercise test were older, included a larger proportion of women, and had previous myocardial infarctions, and more 2- and 3-vessel coronary artery disease (Tables I and II) compared with those who did perform an exercise test. Of 333 conservative and 362 invasive strategy surviving patients who did not perform an exercise test by 14 days after study entry, 59.2% with the conservative strategy and 52.5% with the invasive strategy had experienced ≥ 1 event, defined as reinfarction, recurrent painful ischemic events or newly occurring congestive heart failure, by 14 days. These events occurred significantly less often in patients who performed exercise tests (Table I).

The mortality between 14 days and 1 year after study entry was significantly less in patients able to perform the low-level exercise test than in those that could not (1.4% [17 of 1,241] vs 6.3% [23 of 364] for the invasive strategy [$p < 0.001$], and 2.3% [29 of 1,261] vs 9.3% [31 of 334] for the conservative strategy [$p < 0.001$]; Figure 3).

In the conservative group, the mean rest and exercise ejection fractions were 47.6 and 50.6%, respectively, in patients who exercised to less than stage II, and 48.2 and 53.9%, respectively in those who exercised to stage II. The results were similar in the invasive group. Among 14-day surviving patients who performed the exercise test (Figure 1), angina, decreased ejection fraction $\leq 5\%$ or ST-segment depression ≥ 1 mm on the predischarge exercise test occurred in 226 and 327 patients random-

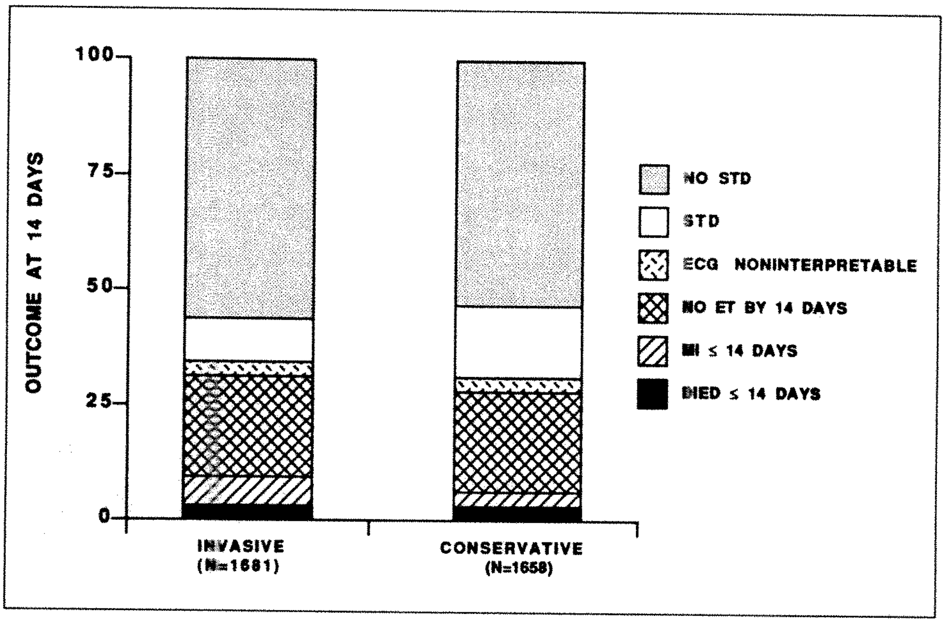

FIGURE 2. Mortality and exercise electrocardiographic outcomes at 14 days according to assigned treatment strategy in TIMI II. $p = 0.57$ for difference in proportion able to exercise without ST depression (STD); $p = 0.03$ for any difference in outcomes. MI = myocardial infarction; other abbreviations as in Figure 1.

TABLE II Findings of Protocol Cardiac Catheterization Among Invasive Strategy Patients According to Whether Exercise Test Was Performed < 14 Days After Study Entry

Protocol Catheterization Finding		Exercise Test (n = 1,241); n (%)	No Exercise Test (n = 362); n (%)	p Value
Protocol cardiac catheterization performed	Yes	1,155 (93.1)	313 (86.5)	0.001
	No	86 (6.9)	49 (13.5)	
No. of vessels with % stenosis ≥ 60%	0	125 (11.2)	30 (10)	0.001
	1	677 (60.5)	132 (44)	
	2	258 (23.1)	95 (31.7)	
	3	59 (5.3)	43 (14.3)	
	Missing*	36	13	
MI-related coronary artery	None	2 (0.2)	6 (1.9)	0.39
	Right	518 (44.8)	131 (41.8)	
	Left main	0 (0)	2 (0)	
	Left anterior descending	495 (42.9)	128 (40.9)	
	Left circumflex	140 (12.1)	46 (14.7)	
	Missing*	0	0	
TIMI grade of MI-related coronary artery†	0	123 (10.7)	38 (12.1)	0.60
	1	45 (3.9)	9 (2.9)	
	2	217 (18.8)	65 (20.8)	
	3	767 (66.6)	201 (64.2)	
	Missing*	3	0	
Collaterals to MI-related coronary artery present	Yes	128 (11.4)	34 (11.3)	0.96
	No	991 (88.6)	266 (88.7)	
	Missing*	35	13	

*Number of patients who underwent protocol cardiac catheterization for whom data item is missing.
†Before percutaneous transluminal coronary angioplasty.
MI = myocardial infarct.

ized to the invasive and conservative strategies, respectively. Of 1,168 patients randomized to the invasive strategy with an interpretable exercise electrocardiogram (Figure 1), 108 had exercise-induced ST-segment depression ≥1 but <2 mm, and 19 had ≥2 mm. Of 1,187 patients randomized to the conservative strategy (Figure 1), 146 had ST-segment depression ≥1 but <2 mm, and 30 had ≥2 mm.

One-year prognosis after exercise testing: No statistically significant differences according to the study criteria were found in either treatment strategy for 1-year occurrence of death, or of death or myocardial infarction according to the presence of specific exercise test outcomes (ST-segment depression or elevation, chest pain, and peak heart rate and systolic blood pressure). In the conservative strategy, 1-year mortality was 0.6 vs 2.4% in patients with versus without exercise-induced ST-segment depression (relative risk 0.2; $p = 0.13$). When exercise-induced ST-segment depression or pain was examined, the 1-year mortality was 1.4 vs 2.3% for

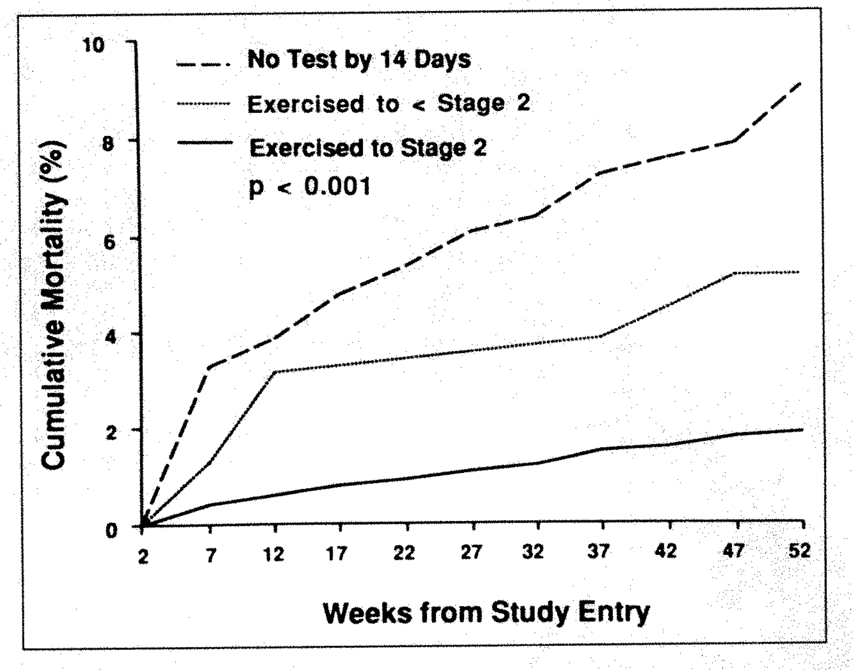

FIGURE 3. Mortality of patients in conservative strategy who did not perform exercise test compared with that of those who were able to complete only 1 or both stages of low-level, predischarge, exercise test ($p < 0.001$).

TABLE III Finding of Protocol Cardiac Catheterization Among Invasive Strategy Patients Surviving > 14 Days with Exercise Electrocardiogram ≤ 14 Days After Entry Read by Electrocardiography Core Laboratory, According to Presence of Exercise ST-Depression

Protocol Catheterization Finding		Total (n = 1,168)	ST Depression (n = 127) n (%)	No ST Depression (n = 1,041) n (%)	p Value
Protocol cardiac catheterization performed	Yes	1,091	118 (92.9)	973 (93.5)	0.80
	No	77	9 (7.1)	68 (6.5)	
No. of vessels with % stenosis ≥ 60%	0	115	5 (4.4)	110 (11.7)	0.001
	1	642	60 (52.6)	582 (61.7)	
	2	243	32 (28.1)	211 (22.4)	
	3	57	17 (14.9)	40 (4.2)	
	Missing*	34	4	30	
MI-related coronary artery	None	2	0 (0)	2 (0.2)	0.001
	Right	490	66 (55.9)	424 (43.6)	
	Left anterior descending	463	26 (22)	437 (44.9)	
	Left circumflex	136	26 (22)	110 (11.3)	
	Missing	0	0	0	
Mean % stenosis of MI coronary artery		75.0	77.9	74.6	0.09
TIMI flow grade of MI coronary artery†	0	117	17 (15)	100 (10.9)	0.14
	1	24	2 (1.8)	22 (2.4)	
	2	99	16 (14.2)	83 (9)	
	3	794	78 (69)	716 (77.7)	
	Missing	57	5	52	
Collaterals to MI coronary artery present	+	121	15 (13.2)	106 (11.2)	0.54
	0	936	99 (86.8)	837 (88.8)	
	Missing	34	4	30	
Protocol PTCA performed or attempted	+	719	66 (52)	653 (62.7)	0.02
	0	449	61 (48)	388 (37.3)	

*Number of patients who underwent protocol cardiac catheterization for whom data item is missing. Percentages based on patients with information for this data item.

†Refers to TIMI grade after PTCA for patients who received protocol PTCA.

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

patients with versus without these findings (relative risk 0.6; p = 0.39).

Among the invasive strategy patients, 1-year mortality in those with versus without exercise-induced ST-segment depression was 3.2 vs 1.2% (relative risk 2.8; p = 0.06). The 1-year mortality was 2.5 vs 1.2% (relative risk 2.1; p = 0.18) for patients with versus without exercise-induced ST-segment depression or chest pain.

ST-segment elevation: Among conservative strategy patients for whom predischarge resting radionuclide ventriculography data were also available, there was a difference in mean resting left ventricular ejection fraction for those without exercise-induced ST-segment changes, and those with ST-segment depression and ST-segment elevation (50.8, 53.6 and 42.5%, respectively; p <0.001); in the invasive strategy patients, mean ejection fraction was 51.8, 52.6 and 41.7% for the 3 groups, respectively (p <0.001). The proportion of patients with an ejection fraction <35% were 10.0, 5.7 and 22.7% for patients without exercise-induced ST-segment changes, and those with ST-segment depression and ST-segment elevation, respectively, among conservative strategy patients. The findings were similar among invasive strategy patients.

There was no statistically significant difference in mean resting ejection fraction between patients with ST-segment depression and no ST-segment changes in either treatment strategy after adjustment for anterior versus nonanterior infarct location. The difference in ejection fraction between patients with ST-segment elevation and depression or no change remained statistically significant (p <0.001) in both strategies after adjustment for infarct location.

Anatomic correlates and impact of coronary revascularization on exercise ST-segment depression in patients randomized to the invasive strategy: The impact of coronary angiographic findings and revascularization on exercise-induced ST-segment depression was examined in the 1,168 patients assigned to the invasive strategy. The percentages of patients with 2- and 3-vessel coronary disease were greater in those with than without exercise-induced ST-segment depression (43.0 vs 26.6%; p <0.001) (Table III). The mean percent stenosis of the infarct-related artery after PTCA was significantly greater in patients with than without exercise-induced ST-segment depression (53.2 vs 43.4%; p <0.001). Patients with exercise-induced ST-segment depression were less likely to have had the left anterior descending coronary artery as the infarct-related vessel. The presence of collaterals and TIMI grade of the infarct-related vessel were not associated with exercise-induced ST-segment depression.

Use of the hospital discharge exercise test to select patients for cardiac catheterization: Hospital discharge exercise test outcomes among conservative strategy patients (excluding those randomized in TIMI II-A whose protocol cardiac catheterization was required)[3] who had not undergone cardiac catheterization before the test were classified locally as positive for 160, negative for 725 and inconclusive for 71. Of these patients, 78 (48.8%) with a positive test, 176 (24.3%) with a negative test and 13 (18.3%) with an inconclusive test underwent cardiac catheterization before the 6-week follow- up visit.

Ventricular arrhythmias: Few patients were observed with isolated premature ventricular beats or more complex ventricular ectopy during exercise. The available evidence did not suggest that these findings were associated with increased 1-year mortality risk.

DISCUSSION

For the purpose of this analysis, an adverse outcome at 14 days was defined by the combined end point of death, presence of exercise-induced ST-segment depression, or inability to perform the exercise test. The percentages of patients with any of these outcomes were similar in the invasive and conservative strategies, although the relative proportions of patients with different adverse outcomes varied; slightly less invasive than conservative strategy patients had ST-segment depression with exercise, and slightly more died or did not exercise. This combined end point for comparison of the 2 treatment strategies was chosen to avoid the biases in comparing strategies based only on the select group of patients who survived 14 days and were able to perform the exercise test. The labeling of inability to perform the exercise test by 14 days as a poor outcome is supported by the large proportion of patients who did not exercise and had cardiovascular events by 14 days, and by the increased 1-year mortality and morbidity in this group compared with those who were able to perform the exercise test.

Prevalence of exercise electrocardiographic abnormalities in TIMI II: In the prethrombolytic era, approximately 30% of patients convalescing from an acute myocardial infarction and undergoing predischarge exercise tests developed ischemic ST-segment depression, and 20% developed angina.[11–13] In TIMI II patients who underwent exercise testing (all of whom had received thrombolytic therapy), the frequency of exercise-induced ST-segment depression was only 10.9% in the invasive strategy and 14.8% in the conservative one. The frequency of exercise-induced ST-segment depression ≥ 0.1 mV among patients in the conservative strategy was 20.4% for nonanterior infarcts and 9.9% for anterior ones. Exercise-induced chest pain occurred in only 4.3 and 5.7% of patients in the invasive and conservative strategies, respectively. There are several reasons why the occurrence of markers of exercise-induced is-chemia may have been less frequent in the TIMI II patients.

The TIMI II protocol required that patients assigned to the invasive strategy undergo cardiac catheterization at 18 to 48 hours after entry, with revascularization if feasible. Patients in the conservative strategy with spontaneous ischemia before hospital discharge were to undergo coronary angiography and revascularization when the anatomy was suitable. Coronary revascularization procedures were performed before the predischarge exercise test in 67.2% of patients assigned to the invasive strategy and in 9.3% assigned to the conservative strategy, reducing the potential to induce ischemia during exercise. All patients in TIMI II received early thrombolytic therapy, which is associated with a greater frequency of early opening of infarct-related vessels than in those who do not receive a thrombolytic drug, and with a reduction in myocardial infarct size. The frequency of 3-vessel coronary artery disease in TIMI II patients assigned to the invasive strategy was 5.3%, which is less than that of historical control subjects who underwent predischarge exercise testing before the widespread use of thrombolytic agents (prevalence of 3-vessel coronary artery disease in earlier studies was 22, 31 and 45%, respectively).[30–32] Exercise-induced myocardial ischemic responses are more frequent in patients with 3-vessel than with 1- or 2-vessel coronary artery disease.

The predischarge exercise test in TIMI II was performed in the supine position for standardized acquisition of gated blood pool studies. Shaw et al[9] reported a greater peak oxygen consumption and a slightly greater frequency of exercise-induced myocardial ischemic responses in 30 postinfarct patients who exercised using a predischarge, upright, low-level, treadmill protocol than in those using a similar supine bicycle ergometry protocol. Thus, several factors may account for the decreased frequency of exercise-induced myocardial ischemic variables in the TIMI II trial compared with in earlier published series.

Prognosis: One-year mortality among patients who performed the exercise test within 14 days of study entry was low among patients assigned to either the invasive (1.4%) or conservative (2.3%) strategies. The relatively low mortality rates in this study compared with the TIMI II 1-year rates reported by Williams et al[33] occur because the latter investigators included patients who died before the exercise test was performed, as well as those who were unable to perform the exercise test shown to have a higher mortality in this series, as well as in other reports.[34] The relatively low incidence of fatal events limited the statistical power to detect differences in prognosis associated with exercise test outcomes among patients who performed the test. The conservative treatment strategy recommended that patients with spontaneous or important exercise-induced ST-segment depression undergo coronary angiography and revascularization when possible. Spontaneous rather than exercise-induced angina during the initial hospitalization was a more frequent indication for coronary angiography.[35] In patients with positive exercise tests, approximately twice as many were likely to undergo coronary revascularization after the exercise test as were those whose tests were considered negative by the Clinical Center. Targeting conservative strategy patients with evidence of important exercise-induced myocardial ischemia for coronary revascularization (PTCA or coronary artery bypass grafting) probably altered the natural history of these high-risk patients, resulting in a very low 1-year mortality comparable to that of patients without exercise-induced angina or ST-segment depression.

Among patients assigned to the invasive strategy, the presence of exercise-induced ST-segment depression was associated with a trend toward an increased 1-year mortality compared with that of those without this finding (relative risk 2.8; $p = 0.06$). Approximately half of the patients in the invasive strategy with ST-segment depression had undergone PTCA by the time the exercise test was performed, and only 5 had had a second procedure (PTCA or coronary artery bypass grafting) by the 6-week exercise test. After the coronary anatomy was known, and PTCA was performed, if technically feasible (or coronary bypass grafting, if the patient was not a suitable PTCA candidate), predischarge, exercise-induced ST-segment depression in patients randomly assigned to the invasive strategy was less likely to influence physicians to recommend additional attempts at coronary revascularization than in those randomly assigned to the conservative strategy.

Exercise-induced ST-segment elevation: Exercise-induced ST-segment elevation was associated with a greater mortality within 1 year, which was similar to previous reports.[32,36] Although the difference was not statistically significant, the relatively short 1-year follow-up and the small number of deaths observed reduced the power of this comparison. Left ventricular function was worse in patients with than without exercise-induced ST elevation. Several studies of acute and chronic ischemic heart disease have demonstrated the relation between increased long-term mortality and decreased left ventricular function.[37,38]

REFERENCES

1. TIMI Research Group. Immediate versus delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction (TIMI IIA results). *JAMA* 1988;260:2849–2858.

2. TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. *N Engl J Med* 1989;320:618–627.

3. Rogers WJ, Baim DS, Gore JM, Brown BG, Roberts R, Williams DO, Chesebro JH, Babb JD, Sheehan FH, Wackers FJT, Zaret BL, Robertson TL, Passamani ER, Ross R, Knatterud GL, Braunwald E. Comparison of immediate invasive, delayed invasive, and conservative strategies after tissue-type plasminogen activator. Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II-A Trial. *Circulation* 1990;81:1457–1476.

4. Campbell S, A'Hern R, Quigley P, Vincent R, Jewitt D, Chamberlain D. Identification of patients at low risk of dying after acute myocardial infarction, by simple clinical and submaximal exercise test criteria. *Eur Heart J* 1988;9:938–947.

5. Fioretti P, Brower RW, Simoons ML, Ten Katen H, Beelen A, Baardman T, Lubsen J, Hugenholtz PG. Relative value of clinical variables, bicycle ergometry, rest radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring at discharge to predict 1 year survival after myocardial infarction. *J Am Coll Cardiol* 1986;8:40–49.

6. Tubau JF, Chaitman BR, Bourassa MG, Waters DD. Detection of multivessel coronary disease after myocardial infarction using exercise stress testing and multiple ECG lead systems. *Circulation* 1980;61:44–52.

7. De Feyter PJ, Van Eenige MJ, Dighton DH, Visser FC, De Jong J, Roos JP. Prognostic value of exercise testing, coronary angiography and left ventriculography 6–8 weeks after myocardial infarction. *Circulation* 1982;66:527–536.

8. Weld FM, Chu KL, Bigger JT Jr, Rolnitzky LM. Risk stratification with low-level exercise testing 2 weeks after acute myocardial infarction. *Circulation* 1981;64:306–314.

9. Shaw LJ, Younis LT, Stocke KS, Sharma AK, Chaitman BR. Effects of posture on metabolic and hemodynamic predischarge exercise response after acute myocardial infarction. *Am J Cardiol* 1990;66:134–139.

10. Krone RJ, Gillespie JA, Weld FM, Miller JP, Moss AJ, and the Multicenter Postinfarction Research Group. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. *Circulation* 1985;71:80–89.

11. Waters DD, Theroux P, Halphen C, Mizgala HF. Clinical predictors of angina following myocardial infarction. *Am J Med* 1979;66:991–996.

12. Williams WL, Nair RC, Higginson LAJ, Baird MG, Allan K, Beanlands DS. Comparison of clinical and treadmill variables for the prediction of outcome after myocardial infarction. *J Am Coll Cardiol* 1984;4:477–486.

13. Theroux P, Waters DD, Halphen C, Debaisieux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;301:341–345.

14. Peart I, Seth L, Albers C, Odemuyiwa O, Hall RJC. Post-infarction exercise testing in patients under 55 years. Relation between ischemic abnormalities and the extent of coronary artery disease. *Br Heart J* 1986;55:67–74.

15. Schwartz KM, Turner JD, Sheffield LT, Roitman DI, Kansal S, Papapietro SE, Mantle JA, Rackley CE, Russell RO, Rogers WJ. Limited exercise testing soon after myocardial infarction. Correlation with early coronary and left ventricular angiography. *Ann Intern Med* 1981;94:727–734.

16. DeBusk RF, Kraemer HC, Nash E, Berger WE, Lew H. Stepwise risk stratification soon after acute myocardial infarction. *Am J Cardiol* 1983;52:1161–1166.

17. Fioretti P, Brower RW, Simoons ML, Bos RJ, Baardman T, Beelen A, Hugenholtz PG. Prediction of mortality during the first year after acute myocardial infarction from clinical variables and stress test at hospital discharge. *Am J Cardiol* 1985;55:1313–1318.

18. Chaitman BR, Waters DD, Corbara F, Bourassa MG. Prediction of multivessel disease after inferior myocardial infarction. *Circulation* 1978;57:1085–1090.

19. Kulick DL, Rahimtoola SH. Risk stratification in survivors of acute myocardial infarction: routine cardiac catheterization and angiography is a reasonable approach in most patients. *Am Heart J* 1991;121:641–656.

20. Grines CL, DeMaria AN. Optimal utilization of thrombolytic therapy for acute myocardial infarction: concepts and controversies. *J Am Coll Cardiol* 1990;16:223–231.

21. Gruppo Italiana per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:349–360.

22. Zaret BJ, Wackers FJ, Terrin ML, Ross R, Weiss M, Slater J, Morrison J, Bourge RC, Passamani E, Knatterud G, Braunwald E. Assessment of global and regional left ventricular performance at rest and during exercise after thrombolytic therapy for myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II Study. *Am J Cardiol* 1992;69:1–9.

23. Caralis DG, Wiens G, Shaw L, Younis LT, Haueisen ME, Wiens RD, Chaitman BR. An off-line digital system for reproducible interpretation of the exercise ECG. *J Electrocardiol* 1990;23:285–291.

24. Caralis DG, Shaw L, Bilgere B, Younis L, Stocke K, Wiens R, Chaitman BR. Application of computerized exercise electrocardiogram digitization interpretation in large clinical trials. *J Electrocardiol* 1992;25:101–110.

25. Kaplan EL, Meier P. Nonparametric observation from incomplete observations. *Journal of the American Statistical Association* 1958;53:457–481.

26. Prentice RL. Linear rank tests with right censored data. *Biometrika* 1978;65:167–179.

27. Cox DR. Regression models and life tables (with discussion). *Journal of the Royal Statistical Society B* 1972;34:187–220.

28. SAS Institute, Inc. SAS User's Guide, Version 5 Ed. Cary, North Carolina: SAS Institute, 1985.

29. Dixon WJ, ed. BMDP Statistical Software Manual. Los Angeles: BMDP Statistical Software, 1988.

30. Miller RR, DeMaria AN, Vismara LA, Salel AF, Maxwell KS, Amsterdam EA, Mason DT. Chronic stable inferior myocardial infarction: unsuspected harbinger of high-risk proximal left coronary arterial obstruction amenable to surgical revascularization. *Am J Cardiol* 1977;39:954–960.

31. Gibson RS, Watson DD, Craddock GB, Crampton RS, Kaiser DL, Denny MJ, Beller GA. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. *Circulation* 1983;68:321–336.

32. Paine TD, Dye LE, Roitman DI, Sheffield LT, Rackley CE, Russell RO, Rogers WJ. Relation of graded exercise test findings after myocardial infarction to extent of coronary artery disease and left ventricular dysfunction. *Am J Cardiol* 1978;42:716–723.

33. Williams DO, Braunwald E, Knatterud G, Babb J, Bresnahan J, Greenberg M, Raizner A, Wasserman A, Robertson T, Ross R, and TIMI Investigators. One-year results of the Thrombolysis in Myocardial Infarction Investigation (TIMI) Phase II Trial. *Circulation* 1992;85:533–542.

34. Froelicher VF, Perdue S, Pewen W, Risch M. Applications of meta-analysis using an electronic spread sheet to exercise testing in patients after myocardial infarction. *Am J Med* 1987;83:1045.

35. Rogers WJ, Babb JD, Baim DS, Chesebro JH, Gore JM, Roberts R, Williams DO, Frederick M, Passamani ER, Braunwald E. Selective versus routine predischarge coronary arteriography after therapy with recombinant tissue-type plasminogen activator, heparin and aspiring for acute myocardial infarction. *J Am Coll Cardiol* 1991;17:1007–1016.

36. Bruce RA, Fisher LD, Pettinger M, Weiner DA, Chaitman BR. ST segment elevation with exercise: a marker for poor ventricular function and poor prognosis: Coronary Artery Surgery Study (CASS) confirmation of Seattle Heart Watch results. *Circulation* 1988;77:897–905.

37. Mock MB, Ringqvist I, Fisher LD, Davis KB, Chaitman BR, Kouchoukos NT, Kaiser GC, Alderman E, Ryan TJ, Russell RO, Mullin S, Fray D, Killip T, and Participants in the Coronary Artery Surgery Study. Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1982;66:562–568.

38. Ringqvist I, Fisher LD, Mock MB, Davis KB, Wedel H, Chaitman BR, Passamani E, Russell RO, Alderman EL, Kouchoukas NT, Kaiser GC, Ryan TJ, Fray D. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest* 1983;71:1854–1866.

Transient Myocardial Ischemia After a First Acute Myocardial Infarction and Its Relation to Clinical Characteristics, Predischarge Exercise Testing and Cardiac Events at One-Year Follow-Up

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The relation between early out-of-hospital ambulatory ST-segment monitoring, clinical characteristics, predischarge maximal exercise testing and cardiac events was determined in 123 consecutive men (age 55 ± 8 years) with a first acute myocardial infarction (AMI). During 36 hours of ambulatory recording 11 ± 5 days after AMI 23 patients (19%) had 123 ischemic episodes (group 1), whereas 100 patients demonstrated no ischemia (group 2). Exercise-induced ST-segment depression was more prevalent in group 1 (83%) than in group 2 (47%) ($p < 0.005$). Group 1 patients also had more severe ischemia as judged from a shorter exercise duration before significant ST-segment depression (5.5 ± 2.4 vs 7.7 ± 4.1 minutes; $p < 0.03$) and more pronounced ST-segment depression on exercise testing (4.1 ± 2.6 vs 2.6 ± 1.6 mm; $p < 0.03$). Furthermore, exercise test results revealed an impaired hemodynamic response in group 1 compared with group 2: systolic blood pressure at maximal work load 160 ± 31 vs 176 ± 28 mm Hg ($p < 0.025$) and systolic blood pressure increase during exercise 41 ± 24 vs 56 ± 22 mm Hg ($p < 0.01$). Within 368 ± 8 days of follow- up the frequency of cardiac events (cardiac death, nonfatal reinfarction, and severe angina including the need of revascularization) was 52% in group 1 compared with 22% in group 2 ($p < 0.01$). Exercise-induced ischemia did not predict an adverse outcome: event rate 30 vs 25% in patients without residual ischemia (p = NS). None of the 5 patients who died had residual ischemia on either ambulatory monitoring or exercise testing. Patients having cardiac death had a significantly lower left ventricular ejection fraction, 32 ± 16% than the 118 survivors, 49 ± 11% ($p < 0.02$).

(Am J Cardiol 1993;71:139–144)

Data comparing the relation between residual ischemia on predischarge exercise testing and early out-of-hospital ambulatory monitoring in patients with a recent first acute myocardial infarction (AMI) are not available. The aim of this study was to determine the baseline characteristics of survivors of AMI with and without transient ischemia on ambulatory recording, and to evaluate the correlation between the results of early postdischarge ambulatory ST-segment monitoring and the findings from predischarge maximal exercise testing. Finally, we wanted to assess the 1-year prognostic significance of residual ischemia and left ventricular ejection fraction in this subset of patients with coronary artery disease.

METHODS

Study patients: The period of patient enrollment was between October 1987 and October 1989. The study population comprised 123 consecutive men <70 years of age who survived a first AMI at our institution. AMI was diagnosed when ≥2 of the following criteria were present: (1) typical chest pain, (2) diagnostic electrocardiographic changes, or (3) diagnostic myocardial enzyme changes. Patients were excluded in case of preadmission chest pain lasting >24 hours, former heart surgery or angioplasty, electrocardiographic conduction defects, atrial fibrillation, insulin-dependent diabetes mellitus, and other noncardiac diseases likely to influence mortality. If Q waves ≥30 ms in ≥2 leads were present, the AMI was classified as Q-wave AMI. Leads I, aVL and V_1 to V_6 were classified as representing myocardium in the anterior wall, and leads II, III and aVF as involving the inferior wall. If serum creatine kinase-MB isoenzyme was ≥20 U/liter and serum lactate dehydrokinase-1-fraction reached ≥170 U/liter, the diagnosis of an AMI was confirmed. Actually, a total of 125 patients fulfilled our inclusion criteria. However, 2 patients had to be excluded from exercise testing and thus final study inclusion, because echocardiography revealed a moderate pericardial effusion in 1, and a large thrombus in the left ventricle in the other. During the inclusion period another 6 patients with a first AMI were precluded from inclusion because of acute intervention before discharge (unstable angina pectoris or ventricular septum rupture, or both).

Exercise testing: One day before discharge all patients performed a maximal symptom-limited bicycle ergometer exercise test with 6 standard limb and 12 pre-

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TABLE I Comparison of Characteristics of Patients Recovering from a First Myocardial Infarction With (group 1) and Without (group 2) Transient Episodes of Myocardial Ischemia During Early Postdischarge Ambulatory Monitoring

	Group 1 (n = 23)	Group 2 (n = 100)
Age (year)*	54 ± 8	55 ± 9
Systemic hypertension	3 (13%)	13 (13%)
Hypercholesterolemia	1 (4%)	5 (4%)
Non-insulin-dependent diabetes mellitus	2 (9%)	8 (8%)
Cigarette smokers	18 (78%)†	53 (53%)†
Previous angina pectoris	11 (48%)	25 (25%)
No. of angina attacks		
≥1 per week	8	14
<1 per week	3	11
NYHA class I before AMI	14 (61%)	78 (78%)

*Mean ± SD.
†p <0.05.
AMI = acute myocardial infarction; NYHA = New York Heart Association.

TABLE II Comparison of In-Hospital Characteristics of Patients Surviving a First Myocardial Infarction With (group 1) and Without (group 2) Transient Episodes of Myocardial Ischemia During Early Postdischarge Ambulatory Monitoring

	Group 1 (n = 23)	Group 2 (n = 100)
Site of AMI		
Anterior	11 (48%)	49 (49%)
Inferior	11 (48%)	42 (42%)
Multiple/indefinite	1 (4%)	9 (9%)
Type of AMI		
Q-wave	11 (48%)	69 (69%)
Non-Q-wave	12 (52%)	31 (31%)
Myocardial enzymes*		
Peak creatine kinase-MB isoenzyme (U/liter)	94 ± 52	101 ± 58
Peak lactate dehydrokinase-1-fraction isoenzyme (U/liter)	867 ± 486	985 ± 585
Thrombolytic therapy	6 (26%)	29 (29%)
Congestive heart failure in CCU	6 (26%)	29 (29%)
Sinus tachycardia	5 (22%)	24 (24%)
Atrial fibrillation	3 (13%)	12 (12%)
Late ventricular fibrillation/tachycardia (>48 hours)	3 (13%)	6 (6%)
Cardiac arrest	4 (17%)	7 (7%)
Post-AMI angina (>72 hours)	4 (17%)	12 (12%)
Reinfarction	0 (0%)	2 (2%)
Left ventricular ejection fraction (%)*	49 ± 13	48 ± 12
Prophylactic medication at discharge		
Aspirin	14 (61%)	54 (54%)
Digoxin	0 (0%)	6 (6%)
Diuretics	2 (9%)	19 (19%)
Calcium antagonists	4 (17%)	9 (9%)
Long-acting nitrates	3 (13%)	8 (8%)
β blockers	2 (9%)	9 (9%)
ACE inhibitors	0 (0%)	2 (2%)
Antiarrhythmics	1 (4%)	1 (1%)

*Mean ± SD.
ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CCU = coronary care unit.

cordial leads.[1] The electrocardiogram was recorded before exercise, at intervals of 1 minute during exercise, at peak exercise, at immediate recovery, and 2, 4, 6 and ≥9 minutes after exercise. Blood pressures were recorded before exercise, at the end of each 3-minute exercise stage, at peak exercise, and at intervals during postexercise recovery along with the electrocardiogram. A total exercise time of 15 minutes was intended. The initial work load was 30 to 40 W according to age, with stepwise increments of the initial work load every third minute until exhaustion, the development of severe chest pain, severe ventricular arrhythmia, or a sustained decrease in systolic blood pressure. The size of ST-segment depression was not used as an end point. The test was considered positive if ≥1 mm of horizontal or downsloping ST-segment depression was measured 80 ms after the J point compared with the baseline electrocardiogram. Significant ST-segment elevation was defined as ≥1 mm of exercise-induced elevation above the rest baseline measured at the J point. Exercise-induced ST-segment elevation was not considered ischemic if it occurred in leads with pathologic Q waves or had upsloping character, or both. All exercise electrocardiograms were reviewed independently by 2 investigators. In cases of disagreement a third independent reading was done and the majority opinion prevailed.

Ambulatory ST-segment monitoring: At hospital discharge, 36-hour ambulatory ST-segment monitoring was initiated. We used a calibrated amplitude-modulated, 2-channel tape recorder (Tracker Reynolds) with a frequency response from 0.05 to 100 Hz. The bipolar leads were placed at the location of maximal ST-segment depression on the exercise test. A V_3(B2)- and a V_5-like (C3) lead was used if no significant ST-segment depression was detected on exercise.[1] The tapes were analyzed visually by a trained technician or 1 investigator at 60 times real-time (Pathfinder II analyzer, Reynolds), and separate trend curves of ST-segment changes and heart rate (ST-segment module, Reynolds) were obtained. Significant ST-segment depression was defined as horizontal or downsloping ST-segment depression ≥1 mm measured 80 ms after the J point and persisting for at least 1 minute. Separation of 1 episode from the next required the electrocardiogram to return to baseline for ≥2 minutes. To be included in the study an episode should be finally evaluated by an electrocardiogram printout (25 mm/s). All trend curves and electrocardiogram printouts were evaluated independently by 1 technician and 1 investigator. In case of disagreement consensus reading by a third cardiologist unaware of patient characteristics was done. The population was divided into those with (group 1) and those without (group 2) significant ST-segment depression on ambulatory monitoring. During the period of ambulatory recording, patients were encouraged to engage in normal daily activities and to keep a diary outlining any episode of typical chest pain.

Echocardiography: Two days before discharge all patients were examined by 2-dimensional echocardiography. A Toshiba 60A echocardiograph equipped with a 3.75 MHz transducer was used. The patients were examined in the supine and left lateral decubitus position and the heart imaged through several acoustic windows (parasternal, apical and subxiphoid view). All examinations were performed and recorded on videotapes by the same investigator. Calculation of left ventricular ejection fraction was done by a cardiologist from another hospital (JB) who was unaware of other patient data, and the measurement was based on the wall motion in-

TABLE III Comparison of Predischarge Exercise Test Characteristics in Patients Recovering from First Myocardial Infarction With (group 1) and Without (group 2) Transient Episodes of Myocardial Ischemia During Early Postdischarge Ambulatory Monitoring

	Group 1 (n = 23)	Group 2 (n = 100)	p Value
Exercise test, days after AMI	8.4 ± 2.1	9.8 ± 5.3	NS
Patient cooperation optimal	22 (96%)	96 (96%)	NS
Hemodynamic exercise variables			
Systolic BP at maximal load (mm Hg)	160 ± 31	176 ± 28	0.025
Systolic BP increase (mm Hg)	41 ± 24	56 ± 22	0.01
Heart rate at maximal load (beats/min)	151 ± 15	153 ± 18	NS
Heart rate increase (beats/min)	73 ± 18	73 ± 19	NS
Maximal work load (W)	137 ± 35	153 ± 38	NS
Exercise-induced ST ↓	19 (83%)	47 (47%)	0.005
Time until 1 mm ST ↓ (min)	5.5 ± 2.4	7.7 ± 4.1	0.03
Maximal size of ST ↓ (mm)	4.1 ± 2.6	2.6 ± 1.6	0.03
Duration of ≥ 1 mm ST ↓ (min)	16.0 ± 7.9	14.2 ± 6.3	NS
Heart rate at 1 mm ST ↓ (beats/min)	114 ± 22	121 ± 27	NS
Heart rate at maximal ST ↓ (beats/min)	142 ± 27	143 ± 29	NS
Exercise-induced angina	7 (30%)	12 (12%)	NS
Time until angina (min)	6.9 ± 1.6	6.8 ± 2.6	NS
Duration of angina (min)	9.4 ± 6.0	7.1 ± 5.3	NS
Heart rate at start of angina (beats/min)	123 ± 12	123 ± 21	NS
Exercise-induced ST ↑	11 (48%)	72 (72%)	0.05
Time until 1 mm ST ↑ (min)	6.3 ± 3.8	7.4 ± 3.9	NS
Maximal size of ST ↑ (mm)	3.0 ± 2.4	2.6 ± 1.2	NS
Duration of ≥ 1 mm ST ↑ (min)	13.3 ± 6.3	14.0 ± 6.0	NS
Heart rate at 1 mm ST ↑ (beats/min)	118 ± 23	121 ± 21	NS
Heart rate at maximal ST ↑ (beats/min)	141 ± 13	143 ± 26	NS
Exercise-induced arrhythmias	5 (22%)	16 (16%)	NS

Values are expressed as mean ± SD.
AMI = acute myocardial infarction; BP = blood pressure; ST ↓ = ST-segment depression; ST ↑ = ST-segment elevation.

dex using a 9-segment model.[2] The motion of the individual segments was semiquantitated as follows: −1 paradoxical motion, 0 akinesia, +1 hypokinesia, +2 normal kinesia, and +3 hyperkinesia. The mean of the 9 scores constituted the wall motion index. Ejection fraction was calculated as the sum of the wall motion index score multiplied with 30.[2] Results of echocardiography were not known to the investigators who were responsible for patient follow-up.

Follow-up: Patients were seen in our outpatient clinic 6 weeks, 3 months, 6 months and 12 months after AMI. All patients were followed according to our routine regimens, which did not include prophylactic use of long-acting nitrates, β blockers or calcium antagonists. Thus, antianginal drugs were only given in response to symptoms, and the presence of significant ischemia on the exercise or ambulatory electrocardiogram was not an indication for anti-ischemic treatment. Coronary angiography was reserved for patients with angina pectoris refractory to medical therapy. The cardiologist who had to decide whether coronary angiography was indicated did not know whether significant ST-segment depression was present during exercise testing or ambulatory monitoring. Cardiac events were defined as cardiac death with or without AMI, nonfatal AMI, severe angina including the need of coronary artery bypass surgery, percutaneous transluminal coronary angioplasty and/or prophylactic treatment with long-acting nitrates, β blockers or calcium antagonists.

Data handling and statistical analysis: Data were prospectively collected on precoded forms and entered into a computer file. Group comparisons of 2 groups were done by *t* test or Mann-Whitney test. Rates were compared by the chi-square test with Yates's correction. When low expected values were found, we used the 2-tailed Fisher's exact test. Throughout the study probability values of <0.05 were regarded statistically significant.

RESULTS

Ambulatory ST-segment monitoring: Within 33 ± 2 (mean ± SD) hours of ambulatory monitoring, 23 of the 123 patients (19%) with AMI demonstrated a total of 123 ischemic episodes. Thus, the extension of Holter recording added 2 more patients, both with a non-Q-wave AMI and 30 ischemic episodes, to the findings during the initial 24 hours of monitoring.[3] In 2 of 123 episodes (2%), ST-segment depression was accompanied by chest pain. The characteristics of ischemic episodes in this extended monitoring period were similar to characteristics previously reported.[3]

Past history: Current cigarette smoking was more prevalent in patients with transient ischemia (Table I). A history of previous angina also tended to be present more frequently in group 1 (p <0.06).

In-hospital characteristics: In-hospital patient characteristics are summarized in Table II. A non-Q-wave infarction tended to be seen more frequently in group 1 patients, but the difference did not reach statistical significance (p <0.10).

Exercise testing: Exercise variables revealed a significantly impaired systolic blood pressure response in patients with than without transient ischemia (Table III). Exercise-induced ischemia was significantly more prevalent in group 1 than in group 2. Patients with ischemia in the ambulatory setting had a lower ischemic thresh-

TABLE IV Frequency of Cardiac Events at One-Year Follow-Up in 123 Survivors of First Acute Myocardial Infarction With (group 1) and Without (group 2) Transient Ischemia During Early Postdischarge Ambulatory Monitoring

No. of Pts. (%)	Group 1 (n = 23)	Group 2 (n = 100)	p Value
Cardiac death	0 (0)	5 (5)	NS
Nonfatal AMI	1 (4)	6 (6)	NS
Severe angina demanding			
CABG and/or PTCA	5 (22)	4 (4)	<0.02
Prophylactic antianginal therapy	8 (35)	10 (10)	<0.01
≥ 1 cardiac event	12 (52)	22 (22)	<0.01

AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; PTCA = percutaneous transluminal coronary angioplasty.

TABLE V Value of Significant ST-Segment Depression on Predischarge Exercise Testing (ExST ↓), Ambulatory Monitoring (AmST ↓) and Combinations of the Methods in Predicting Cardiac Events Within One Year After First Acute Myocardial Infarction

	ExST ↓ (n = 66)	AmST ↓ (n = 23)	ExST ↓ and AmST ↓ (n = 19)	ExST ↓ and/or AmST ↓ (n = 70)
Sensitivity (%)	59	35	32	62
Specificity (%)	48	88	91	45
Predictive value of a positive test (%)	30	52	58	30
Predictive value of a negative test (%)	75	78	78	75

TABLE VI Characteristics at One-Year Follow-Up (day 368 ± 8) in Patients With (group 1) and Without (group 2) Transient Ischemia During Early Postdischarge Ambulatory Monitoring

	Group 1 (n = 23)	Group 2 (n = 95)	p Value
Heart rate in resting electrocardiogram (beats/min)*	70 ± 12	66 ± 10	NS
Systolic BP (mm Hg)*	131 ± 20	133 ± 18	NS
Current smoker	12 (52%)	40 (42%)	NS
Angina pectoris	10 (43%)	13 (14%)	0.01
NYHA class I	11 (48%)	67 (71%)	NS
Digoxin	2 (9%)	6 (6%)	NS
Diuretics	4 (17%)	12 (13%)	NS
Calcium antagonists	8 (35%)	10 (11%)	0.01
Long-acting nitrates	6 (26%)	8 (8%)	0.05
β blockers	5 (22%)	10 (11%)	NS
≥ 1 anti-ischemic drug	11 (48%)	19 (20%)	0.02
ACE inhibitors	3 (13%)	4 (4%)	NS
Antiarrhythmics	2 (9%)	3 (3%)	NS
Coronary angiography	6 (26%)	6 (6%)	0.03
Left ventricular ejection fraction (%)*	59 ± 14	48 ± 18	NS
1-vessel disease (> 50%)	3	1	NS
2- to 3-vessel disease (> 50%)	3	5	

*Mean ± SD.
Abbreviations as in Tables I to III.

old as judged from the exercise duration before significant ischemia, and group 1 patients also demonstrated more pronounced ST-segment depression during exercise. On stress testing, 14 of the 19 patients with ischemia in the ambulatory setting had ischemia in lead V_5 (C3), whereas 1 had ischemia in lead V_3 (B2). In addition, 1 patient had ischemia in lead D3.[1] The remaining 3 patients with ambulant ischemia revealed no exercise-induced ischemia in the 12 precordial leads, but exclusively in the inferior limb leads. The 19 patients with ischemia during both electrocardiographic methods attained a heart rate at maximal ST-segment depression on Holter recording (96 ± 20 beats/min^{-1}), which was significantly lower than the ischemic threshold on exercise testing (114 ± 22 beats/min^{-1}) ($p < 0.02$). Only 4 of 57 patients (7%) without exercise- induced ischemia had significant ST-segment depression on Holter recording. Exercise-induced ST-segment elevation typically occurred in leads with pathologic Q waves or the changes had upsloping character, or both.

One-year follow-up: Thirty-four patients (28%) had experienced at least 1 cardiac event at 1-year follow-up (Table IV). In patients with transient ischemia, 12 (52%) had at least 1 cardiac event as compared with 22 (22%) of those without ischemic episodes ($p < 0.01$). In 66 patients with exercise-induced ischemia, 20 (30%) experienced at least 1 cardiac event versus 14 (25%) in 57 patients without ischemia (p = NS). None of the 5 patients who died during follow-up demonstrated residual ischemia on ambulatory recording or predischarge exercise testing. If the 2 electrocardiographic methods were combined and a positive test result was defined by the presence of significant ST-segment depression during both techniques (19 patients) and a negative test result was defined by the absence of significant ST-segment depression during 1 or both methods (104 patients), the following results were attained: 11 patients (58%) with residual ischemia had at least 1 cardiac event versus 23 patients (22%) with a negative test result ($p < 0.01$). The value of the 2 methods in predicting cardiac events are summarized in Table V. One of 4 patients with ischemia only in the ambulatory setting had a cardiac event during follow-up (angina pectoris demanding prophylactic medical treatment).

Left ventricular ejection fraction in patients with subsequent cardiac events was 47 ± 13% compared with 48 ± 12% in patients without cardiac events (p = NS). However, a significantly lower ejection fraction could be demonstrated in the 5 patients who died (32 ± 16%) than in the 118 survivors (49 ± 11%) ($p < 0.02$). Furthermore, a left ventricular ejection fraction ≤30% was present in 3 of 5 patients (60%) who died of heart disease within 1 year versus 10 of 118 patients who did not (8%) ($p < 0.01$). In Table VI the clinical characteristics at 1-year follow-up are summarized.

DISCUSSION

Limited data are available regarding the relation between transient ischemia in patients recovering from a recent AMI, and various clinical characteristics.[4–9] The data from patients with stable angina[10–12] may not be representative for early post-AMI patients, as the ischemic burden may be affected by the acute loss of myocardium,[13,14] increased mental stress[15] and disturbances in the autonomic balance.[16] Therefore, we prospectively set out to determine the relation between the results of Holter ST-segment monitoring, clinical characteristics and predischarge exercise testing in a population of consecutive survivors of first AMI. Our final aim was to assess the prognostic significance of residual myocardial ischemia and left ventricular function during 1-year follow-up.

Nineteen percent of the patients demonstrated ischemia during Holter recording, and 98% of episodes were silent. In previous post-AMI studies, a prevalence of transient ischemia ranging from 14 to 46% has been reported.[4–9] The reasons for these inconsistent findings are probably differences in patient groups and study design. Postinfarction patients with and without ischemia on ambulatory monitoring had similar major clinical characteristics including left ventricular ejection fraction at rest. However, exercise-induced ischemia was significantly more prevalent and severe in patients who also had ischemia in the ambulatory setting. Furthermore, these patients demonstrated a limited hemodynamic response on exercise testing. Therefore, the results of our study imply that exercise variables, which have previously been shown to be of prognostic importance in survivors of AMI,[17–20] are associated with the presence of transient ischemia during ambulatory monitoring. The limited hemodynamic response in group 1 patients probably reflects the deleterious effect of the increased total ischemic burden on left ventricular function.[13,21]

The importance of the maximal size of ST-segment depression during exercise testing is still a matter of discussion. In some studies this variable has been related to the anatomic severity of coronary artery disease,[22,23] but its prognostic significance is uncertain.[18,20,24] Conflicting opinions also exist regarding the significance of exercise-induced ST-segment elevation on stress testing in patients with a prior AMI.[25–27] In the present study, ST-segment elevation on exercise testing was significantly more frequent in patients without ambulant ischemia.

Previous studies have demonstrated an adverse outcome in different subgroups of patients with prior AMI and transient ischemia on ambulatory monitoring.[4,5,8,9,28] The results of our study indicate that the presence of ischemic episodes during early out-of-hospital daily activities after a first AMI also is associated with a higher frequency of subsequent cardiac events. Thus, 52% of patients with transient ischemia had at least 1 cardiac event within 1-year follow-up compared with 22% among patients without ischemic changes ($p < 0.01$). In the present study, the location of electrocardiographic leads for ambulatory recording was guided by the results from the preceding exercise test. With use of this design, the presence of ischemia during daily life carried short-term prognostic information supplementary to that of exercise testing. However, it should be emphasized that none of the 5 patients who died of heart disease had myocardial ischemia during either exercise testing or ambulatory monitoring. Actually, only a few studies have reported a significant association between the presence of ST-segment depression on post- AMI exercise testing or Holter recording and mortality as sole end point at 1-year follow-up.[4,8,18,29] Because ST-segment depression — whether silent or not — reflects myocardial ischemia, the significant relation to subsequent symptomatic ischemic events found in the present study may, after all, just confirm what one most logical might expect. Furthermore, the prognosis after a first AMI is highly related to the amount of myocardial damage.[30] In agreement with these findings, our study demonstrated a significant association between a low left ventricular ejection fraction and 1-year mortality. Finally, ST-segment depression on Holter monitoring has previously been reported to occur relatively rarely in patients with poor left ventricular function.[12]

From the results of the present study we do not believe that ambulatory ST-segment monitoring should be performed routinely in patients recovering from a first AMI. However, in patients with residual myocardial ischemia on predischarge maximal exercise testing, Holter ST-segment recording may serve as an option in further risk stratification in relation to subsequent ischemic events.

REFERENCES

1. Fox KM, Deanfield J, Ribero P, England D, Wright C. Projection of ST segment changes on to the front of the chest. Practical implications for exercise testing and ambulatory monitoring. *Br Heart J* 1982;48:555–559.

2. Berning J, Steensgaard-Hansen F. Early estimation of risk by echocardiographic determination of wall motion index in an unselected population with acute myocardial infarction. *Am J Cardiol* 1990;65:567–576.

3. Mickley H, Pless P, Nielsen JR, Møller M. Circadian variation of transient myocardial ischemia in the early out-of-hospital period after first acute myocardial infarction. *Am J Cardiol* 1991;67:927–932.

4. Gottlieb SO, Gottlieb SH, Achuff SC, Baumgardner R, Mellits ED, Weisfeldt ML, Gerstenblith G. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. *JAMA* 1988;259:1030–1035.

5. Ouyang P, Chandra NC, Gottlieb SO. Frequency and importance of silent myocardial ischemia identified with ambulatory electrocardiographic monitoring in the early in-hospital period after acute myocardial infarction. *Am J Cardiol* 1990;65:267–270.

6. Currie P, Saltissi S. Transient myocardial ischaemia after acute myocardial infarction. *Br Heart J* 1990;64:299–303.

7. Nürnberg M, Biber B, Buchelt M, Steinbach K. Stumme Ischämie im Langzeit-EKG der frühen Postinfarktperiode. *Wien Klin Wochenschr* 1989;101: 580–583.

8. Bonaduce D, Petretta M, Lanzillo T, Vitagliano G, Bianchi V, Conforti G, Morgano G, Arrichiello P. Prevalence and prognostic significance of silent myocardial ischaemia detected by exercise test and continuous ECG monitoring after acute myocardial infarction. *Eur Heart J* 1991;12:186–193.

9. Petretta M, Bonaduce D, Bianchi V, Vitagliano G, Conforti G, Rotondi F, Themistoclakis S, Morgano G. Characterization and prognostic significance of silent myocardial ischemia on predischarge electrocardiographic monitoring in unselected patients with myocardial infarction. *Am J Cardiol* 1992;69:579–583.

10. Mulcahy D, Keegan J, Sparrow J, Park A, Wright C, Fox K. Ischemia in the ambulatory setting — the total ischemic burden: relation to exercise testing and investigative and therapeutic implications. *J Am Coll Cardiol* 1989;14:1166–1172.

11. Campbell S, Barry J, Rocco MB, Nabel EG, Mead-Walters K, Rebecca GS, Selwyn AP. Features of the exercise test that reflect the activity of ischemic heart disease out of hospital. *Circulation* 1986;74:72–80.

12. Quyyumi A, Crake T, Wright C, Mockus L, Fox K. The role of ambulatory ST-segment monitoring in the diagnosis of coronary artery disease: comparison with exercise testing and thallium scintigraphy. *Eur Heart J* 1987;8:124–129.

13. Chierchia S, Lazzari M, Freedman B, Brunelli C, Maseri A. Impairment of myocardial perfusion and function during painless myocardial ischemia. *J Am Coll Cardiol* 1983;1:924–930.

14. Levy RD, Shapiro LM, Wright C, Mockus LJ, Fox KM. The haemodynamic significance of asymptomatic ST-segment depression assessed by ambulatory pulmonary artery pressure monitoring. *Br Heart J* 1986;56:526–530.

15. Deanfield JE, Shea M, Kensett M, Horlock P, Wilson RA, de Landsheere CM, Selwyn AP. Silent myocardial ischaemia due to mental stress. *Lancet* 1984; 2:1001–1005.

16. Lombardi F, Sandrone G, Pernpruner S, Sala R, Garimoldi M, Cerutti S, Baselli G, Pagani M, Malliani A. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. *Am J Cardiol* 1987;60:1239–1245.

17. Nielsen JR, Mickley H, Damsgaard EM, Frøland A. Predischarge maximal exercise test identifies risk for cardiac death in patients with acute myocardial infarction. *Am J Cardiol* 1990;65:149–153.

18. Théroux P, Waters DD, Halphen C, Debaisieux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979; 301:341–345.

19. Murray DP, Salih M, Tan LB, Derry S, Murray RG, Littler WA. Which exercise test variables are of prognostic importance post-myocardial infarction? *Int J Cardiol* 1988;20:353–363.

20. Jennings K, Reid DS, Hawkins T, Julian DJ. Role of exercise testing early after myocardial infarction in identifying candidates for coronary surgery. *Br Med J* 1984;288:185–187.

21. Geft IL, Fishbein MC, Ninomiya K, Hashida J, Chaux E, Yano J, Y-Rit J, Genov T, Shell W, Ganz W. Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis. *Circulation* 1982;66:1150–1153.

22. Goldman S, Tselos S, Cohn K. Marked depth of ST-segment depression during treadmill exercise testing. Indicator of severe coronary artery disease. *Chest* 1976;69:729–733.

23. Sanmarco ME, Pontius S, Selvester RH. Abnormal blood pressure response and marked ischemic ST-segment depression as predictors of severe coronary artery disease. *Circulation* 1980;61:572–578.

24. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary artery disease. Selection by univariate and multivariate analyses from the clinical electrocardiographic, exercise, arteriographic and quantitative angiographic evaluations. *Circulation* 1979;59:421–430.

25. Haines DE, Beller GA, Watson DD, Kaiser DL, Sayre SL, Gibson RS. Exercise-induced ST-segment elevation 2 weeks after uncomplicated myocardial infarction: contributing factors and prognostic significance. *J Am Coll Cardiol* 1987; 9:996–1003.

26. Gewirtz H, Sullivan M, O'Reilly G, Winter S, Most AS. Role of myocardial ischaemia in genesis of stress-induced ST segment elevation in previous anterior myocardial infarction. *Am J Cardiol* 1983;51:1289–1293.

27. Fox KM, Jonathan A, Selwyn A. Significance of Exercise Induced ST segment elevation in patients with previous myocardial infarction. *Br Heart J* 1983;49:15–19.

28. Tzivoni D, Gavish A, Zin D, Gottlieb S, Moriel M, Keren A, Banai S, Stern S. Prognostic significance of ischemic episodes in patients with previous myocardial infarction. *Am J Cardiol* 1988;62:661–664.

29. de Belder M, Skehan D, Pumphrey C, Khan B, Evans S, Rothmann M, Mills P. Identification of a high risk subgroup of patients with silent ischaemia after myocardial infarction: a group for early therapeutic revascularization? *Br Heart J* 1990;63:145–150.

30. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331–336.

Continuously Updated 12-Lead ST-Segment Recovery Analysis for Myocardial Infarct Artery Patency Assessment and Its Correlation with Multiple Simultaneous Early Angiographic Observations

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Early angiography may not adequately subgroup patients with myocardial infarction if cyclic changes in coronary flow occur frequently. From a pilot experience using a new 12-lead ST-segment monitor, a continuously updated, self-referenced ST-recovery analysis method was developed to quantify both instantaneous recovery, as a noninvasive marker of patency, and cumulative ST recovery over time, as a marker of the speed, stability and duration of reperfusion. In 22 patients with acute infarction in whom 44 observations of unique angiographic patency were noted within 6 hours of presentation, serial patency assessments simultaneous with all angiographic observations predicted coronary occlusion with 90% sensitivity and 92% specificity. Of the 22 patients, 11 (50%) had multiple ST trend transitions suggesting cyclic changes in coronary flow before catheterization. Speed, stability and duration of ST-segment recovery were defined by the time to first 50% ST recovery, total number of ST-trend transitions and patent physiology index (percentage of monitoring period showing ST recovery), respectively. Subgrouped angiographically, the median (interquartile range) for cumulative ST parameters with patent (n = 8) versus occluded (n = 14) arteries were, respectively — time to 50% recovery, 1.57 (1.16, 1.70) versus 0.17 (−0.47, 0.32) hours; number of reelevation/recovery events, 1.5 (1, 3) versus 3 (1, 3); and patent physiology index, 52 (47, 59) versus 50 (5, 73). Thus, continuous ST-segment recovery analysis appears to predict simultaneous angiographic patency over serial assessments, whereas cumulative parameters appear to contain independent information, probably because of patency changes before or after angiography. (Am J Cardiol 1993;71:145–151)

Angiographically defined patency provides only a brief anatomic visualization of the infarct artery during the course of ongoing infarction. More prolonged angiography has shown that cyclic or "unstable" infarct artery patency is common and consistently related to dynamic ST-segment changes.[1,2] Quantification of the ST-segment recovery process may provide both an instantaneous method for serial patency assessments and a cumulative measure of the speed and stability of reperfusion. Analytic methods for ST analysis in patients presenting with abnormal ST levels subject to sudden marked changes are limited.[3–7] To address this need, we developed a method of self-referenced, continuously updated ST-segment recovery analysis paired with a new 12-lead digital ST monitor and examined its performance in patients who underwent acute angiography during myocardial infarction. The goal of this retrospective analysis was to examine, in a preliminary fashion, the relation of ST-recovery analysis to simultaneous infarct artery patency and the relation of cumulative ST recovery reflecting speed, stability and duration of reperfusion to acute angiographic patency.

METHODS

Patient selection: All patients presented with chest pain within 6 hours and ST-segment elevation not reversed with nitrates, as previously detailed.[8] All patients had myocardial infarction by enzyme elevation and all underwent cardiac catheterization within 6 hours of admission. Choice of therapy and timing of catheterization were determined either through physician judgment or through the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 5 protocol.[9] ST-segment monitoring data were not accessible to the bedside caretakers in any case.

Angiographic analysis: For this analysis the infarct artery was defined as patent with Thrombolysis in Myocardial Infarction (TIMI) trial 2 to 3 flow, or as occluded with TIMI trial 0 to 1 flow. Unique angiographic observations were included for every patient in whom patency change (from patent to occluded or vice versa) occurred during catheterization, either spontaneously or as a result of further therapy. TIMI flow was determined by experienced angiographers (non-TAMI patients) or by the TAMI Angiographic Core Laboratory at the University of Michigan (TAMI 5 patients). In all cases

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angiographic interpretation was made with no knowledge of ST-recovery data.

ST-segment monitoring: The Mortara ST Monitoring System (Mortara Instrument, Milwaukee) has been described in detail previously.[3,4,8] In brief, the device meets American Heart Association criteria for frequency response and sampling rate in standard electrocardiographic carts.[10] A 12-lead electrocardiogram is automatically acquired every 17 seconds, digitized and immediately compared with the patient's own baseline electrocardiogram for ST-segment changes over time in any lead(s). All measurements derive from median beats at J+60 ms. For the pilot experience, all clinical alarms were disabled. In all patients ST monitoring was initiated with impedance-monitored skin preparation (Quik Prep, Quinton Medical, Seattle, Washington) using radiolucent lead wires and electrodes. A total of 10 electrodes were placed over the standard 6 precordial positions, with the 4 limb leads placed on the bony clavicles and iliac crests ("monitoring position") to stabilize baseline. Lead positions remained fixed throughout the monitoring period. Monitoring was initiated before or as

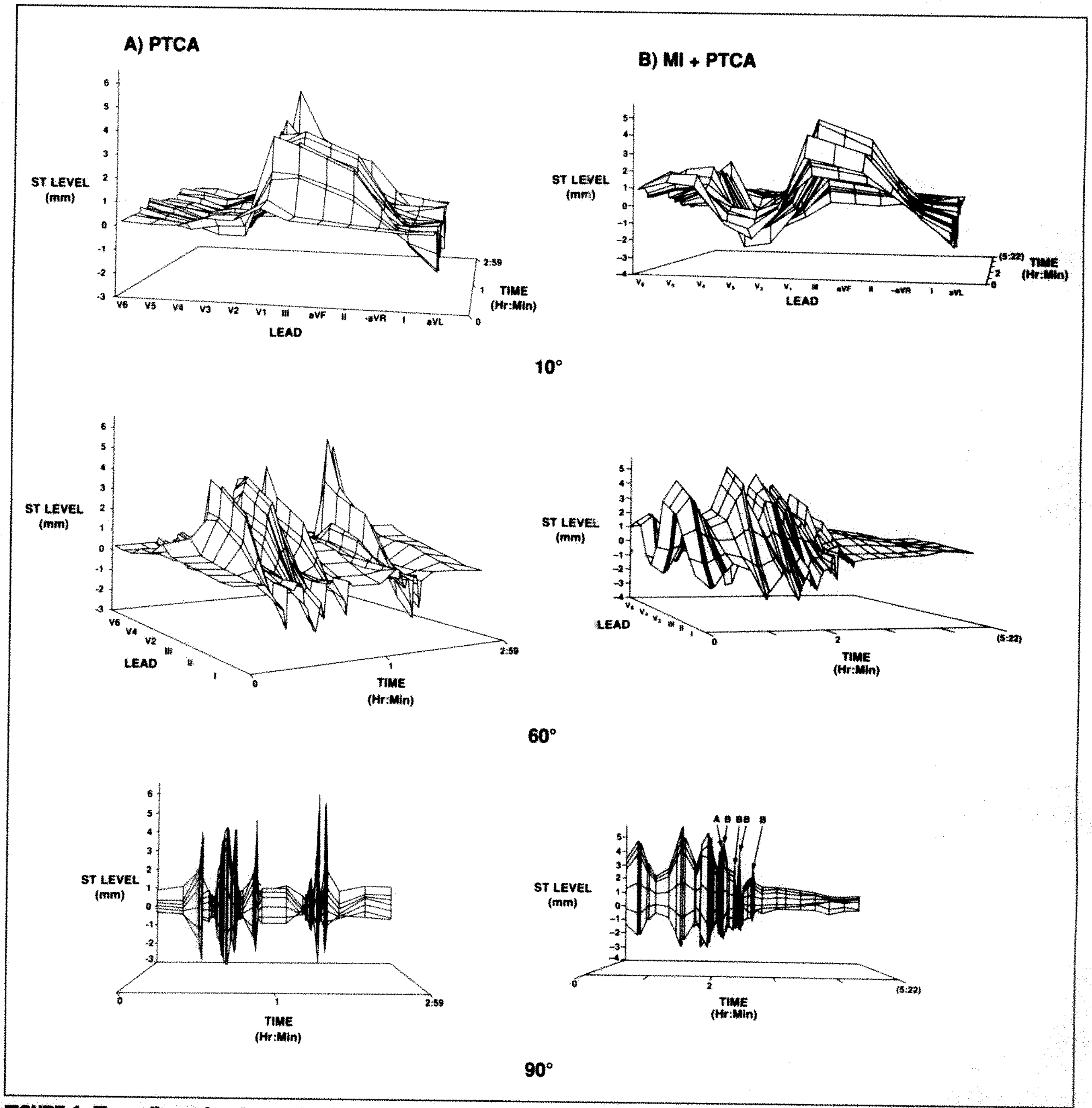

FIGURE 1. Three-dimensional graphic display of digital 12-lead ST-segment data trended as ST level *(Y-axis)* over each of the 12 standard electrocardiographic leads *(X-axis)*, over time *(Z-axis)*, shown in 3 spatial rotations (10°, 60°, 90° from *top to bottom*) for each of 2 patients. *A*, during elective percutaneous transluminal coronary angioplasty (PTCA) of the right coronary patterns from 7 balloon inflations create 7 episodes of ST (re-)elevation in identical precordial "fingerprint" pattern followed by ST recovery with each balloon deflation. The "peak and trough" pattern of transitions over time is the paradigm for reperfusion/reocclusion. *B*, same graphic display in a patient with inferior infarction treated with primary angioplasty. Multiple ST transitions in matched fingerprint pattern occur spontaneously for over 2 hours before initial angiography *(A)*, which revealed an occluded right coronary, reperfused by emergency balloon inflations *(B)*. MI = myocardial infarction.

soon after the onset of therapy as possible. Exclusions from our retrospective analysis included hookup of the ST monitor >60 minutes after onset of therapy or interruption of the ST information by persistent noise, bundle branch block, ventricular rhythm or ventricular pacemaker. All patients were kept at bed rest.

ST-recovery scanning and analysis technique:* All stored electrocardiographic data were downloaded to a personal computer and analyzed with custom-written scanning software which we have previously described.[3] All studies were analyzed over the first 6 hours, including the time of angiography. Patterns of ST recovery and reelevation associated with cyclic flow changes were derived from previous experience with angioplasty balloon inflation and deflation.[4,11–13] Similarities are graphically illustrated in Figure 1. The absence of a predefined "baseline" in the myocardial infarction presentations, however, mandated modifications for quantitative measurements.

The 3-dimensional graphic display in the scanning software illustrated in Figure 1 was used to define each patient's ST measurement matrix. The measurement matrix was taken as the single most abnormal lead in the most abnormal electrocardiogram unless the lead location changed over the course of monitoring or multiple precordial zones (where anterior zone = V_1–V_4; low lateral zone = V_5–V_6; high lateral zone = I, aVL; and inferior zone = II, III and aVF) showed ST elevation simultaneously. With either of these exceptions, the measurement matrix was taken as the summated absolute deviation over the entire 12 leads. Graphic display was also used to identify each patient's multilead pattern of ST activity, or ST "fingerprint."[13] Episodes of recurrent ST deviation were taken as evidence of infarct artery reocclusion only when the fingerprint pattern recurred.[13]

Quality control of the ST matrix and graphic displays was afforded by full disclosure 12-lead superimposition scanning within the analysis software. Every standard 12-lead electrocardiogram was directly visualized in the Duke Ischemia Monitoring Core Laboratory for all studies.

Analysis of ST recovery centered on definition of "troughs" and "peaks" in the trend of the ST-matrix level over time (Figure 2). Troughs and peaks represented points of transition from ST recovery to worsening or from worsening to recovery, respectively. A transition peak was defined as the most abnormal ST level directly preceding any single period of ST-segment recovery. ST-segment recovery was defined as resolution within a 3-hour period consisting of either (1) ≥50% recovery from the immediately preceding peak ST level

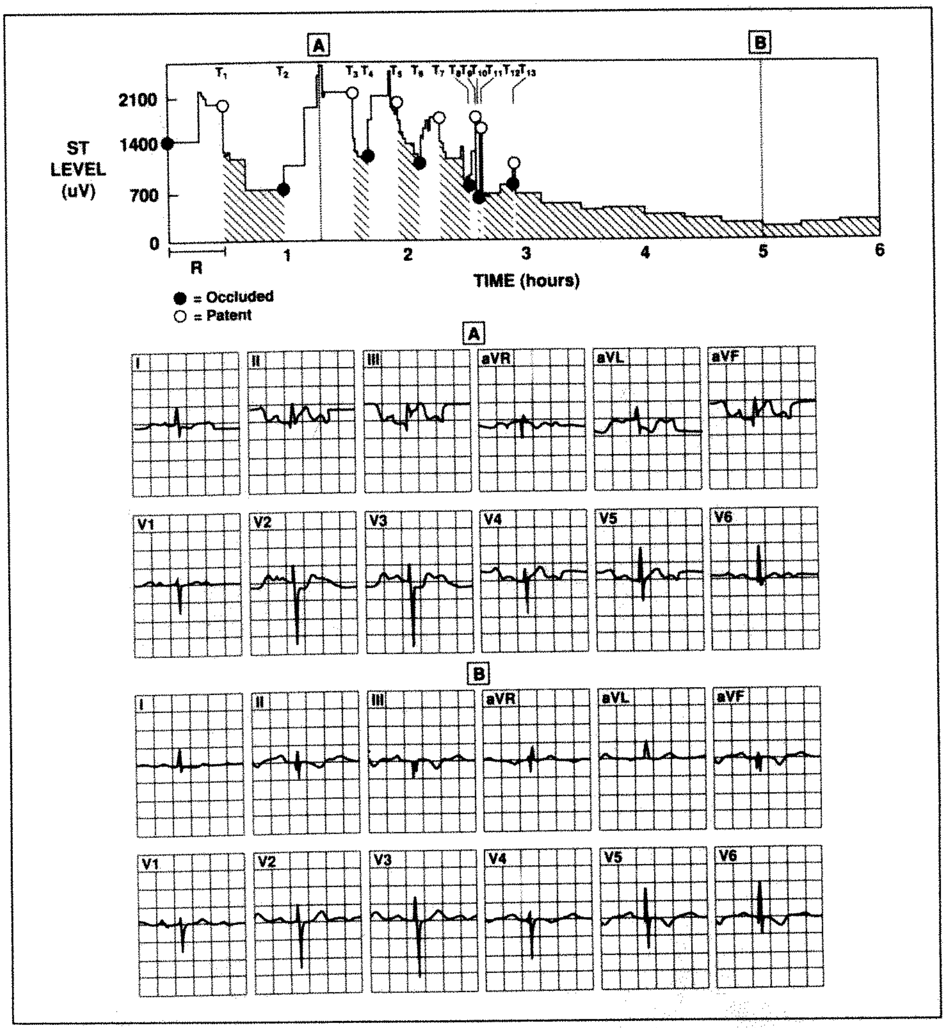

FIGURE 2. Two-dimensional ST-matrix trend from patient in Figure 1B. Time from onset of monitoring to first ST recovery is shown as the interval R. Transition points (T_1 to T_{13}) associated with peaks and troughs are identified as changes from ST recovery to reelevation or vice versa. Patent physiology index equals the sum of the duration of the *shaded* recovery intervals divided by the entire monitoring period. All trend points represent standard 12-lead electrocardiographic information, as illustrated below the trend, which is confirmed using superimposition scanning.

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*See Appendix for summary of definitions.

or (2) 35 to 49% recovery relative to the immediately preceding transition peak; and ≥50% recovery relative to the most abnormal peak documented at any time in the study before the current electrocardiogram. The current electrocardiogram was defined as the electrocardiogram corresponding to each moment an ST-recovery analysis was performed.

A transition trough was defined as the most normalized ST level preceding any single period of ST-segment reelevation. ST-segment reelevation was defined as reelevation in a matched precordial "fingerprint,"[13] evolving over ≤60 minutes and lasting for ≥60 seconds. Minimal amplitude of reelevation was required to be ≥150 μV in any 2 leads or ≥200 μV in a single lead or to a level equal to or greater than the level of the most recent transition peak.

Recovery intervals were defined as beginning at the moment of 50% ST recovery and ending at the onset of reelevation. The time to first 50% ST recovery was defined as the time from the onset of therapy to the onset of the first recovery interval up to a maximum of 6 hours if no such recovery occurred within the monitoring period. The patent physiology index was taken as the percentage of the monitoring period showing ST recovery, defined as the summated duration of all recovery intervals divided by the total monitoring duration ×100. The total number of peaks and troughs from the onset of monitoring to the first contrast injection was taken as the "number of transitions."

Patency assessment at the moment of angiography: Periods of ST recovery were interpreted as the result of reperfusion and periods of persistent (or re-)elevation were interpreted as the result of (re-)occlusion. Periods of incomplete ST transition were interpreted as indeterminate patency. In all patients, an ST-recovery analysis patency prediction was logged simultaneously with the first contrast injection of the infarct artery. In all patients with subsequent unique angiographic observations (as previously defined), additional ST-recovery predictions were logged at each of those times.

Statistical methods: All categorical data are reported as n (%). Because many of the continuous variables are not normally distributed, they are reported as 50th (mean 25th, 75th) percentiles. Ranges are often also included. Only descriptive data are reported, and no statistical tests were performed.

RESULTS

All 22 patients from our pilot experience meeting the criteria were analyzed for this report. The infarct artery was the left anterior descending in 12, the circumflex in 2, and the right coronary artery in 8. Acute therapy consisted of only thrombolytic drugs in 10, only angioplasty in 2, and both in 10. Median time from chest pain onset to initiation of ST monitoring was 4.3 (2.9, 7.6) hours. Median time from ST monitoring to onset of acute therapy was −0.8 (−1.8, 0.3) hours.

At the first contrast injection the infarct artery was patent in 8 (36%) and occluded in 14 (64%) patients. At least 1 period of ST recovery was seen before angiography in 8 patients (100%) with patent arteries, and in 11 (79%) with occluded vessels. More than 2 transitions to reelevation or recovery were seen before catheterization in 3 patients (38%) with patent arteries, and in 8 (57%) with occluded vessels. The 50th, 25th and 75th percentiles, and ranges for time to first 50% ST recovery, the number of transitions over the monitoring period, and patent physiology index in patients with patent versus occluded arteries are shown in Figure 3. Patients with angiographically occluded vessels had a somewhat shorter time interval from onset of therapy to some evidence of transient reperfusion than did patients with

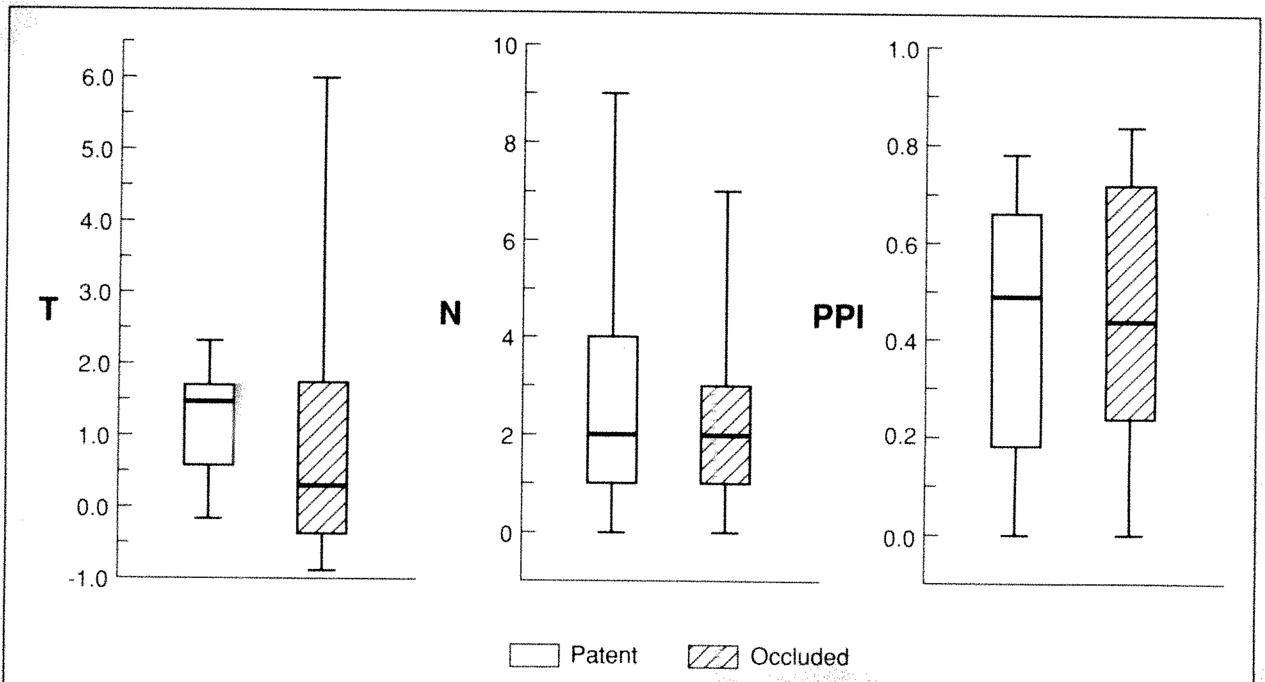

FIGURE 3. Range, 50th, 25th and 75th percentile values of time to first ST recovery (T), number of trend transitions (N), and patent physiology index (PPI) shown subgrouped by coronary patency status at initial angiography.

patent vessels. The stability of reperfusion and duration of reperfusion physiology over the 6 hours monitored were similar whether the initial angiogram showed a patent vessel or an occluded one.

In all 22 patients, <50% ST recovery or ST reelevation was 100% sensitive and specific for simultaneous angiographic occlusion on first contrast injection. Of the 44 angiographically documented patency changes in these 22 patients, sensitivity and specificity for angiographic occlusion were 90 and 92%, respectively.

In 16 of our 22 patients, ST-segment monitoring was initiated before therapy. Of these 16 patients, ST-segment recovery occurred at least once before therapy (suggesting spontaneous reperfusion) in 5 (31%) (Figure 1B).

DISCUSSION

The major findings of this study are twofold. First, serial instantaneous assessments of ST-segment recovery using continuously updated reference points appears to predict simultaneous infarct artery patency, even over multiple changes of patency. Second, patency defined acutely by a single angiographic procedure does not appear to correlate with the rate, stability and duration of ST recovery quantified cumulatively over time periods broader than the catheterization itself. We interpret these findings to indicate that unstable ST-segment recovery reflects cyclic flow changes in the infarct vessel that may occur before, during or after the brief period of time documented by angiography. In our study group, 50% of patients exhibited ST-segment evidence of cyclic flow before catheterization. The incidence of this observation is similar across all 5 other studies that have used continuous electrocardiographic monitoring early in myocardial infarction.[1,2,5–7] Of our 16 patients in whom ST monitoring was begun before therapy, 31% showed evidence of spontaneous reperfusion, similar to our findings in previous work.[11] This spontaneous behavior suggests

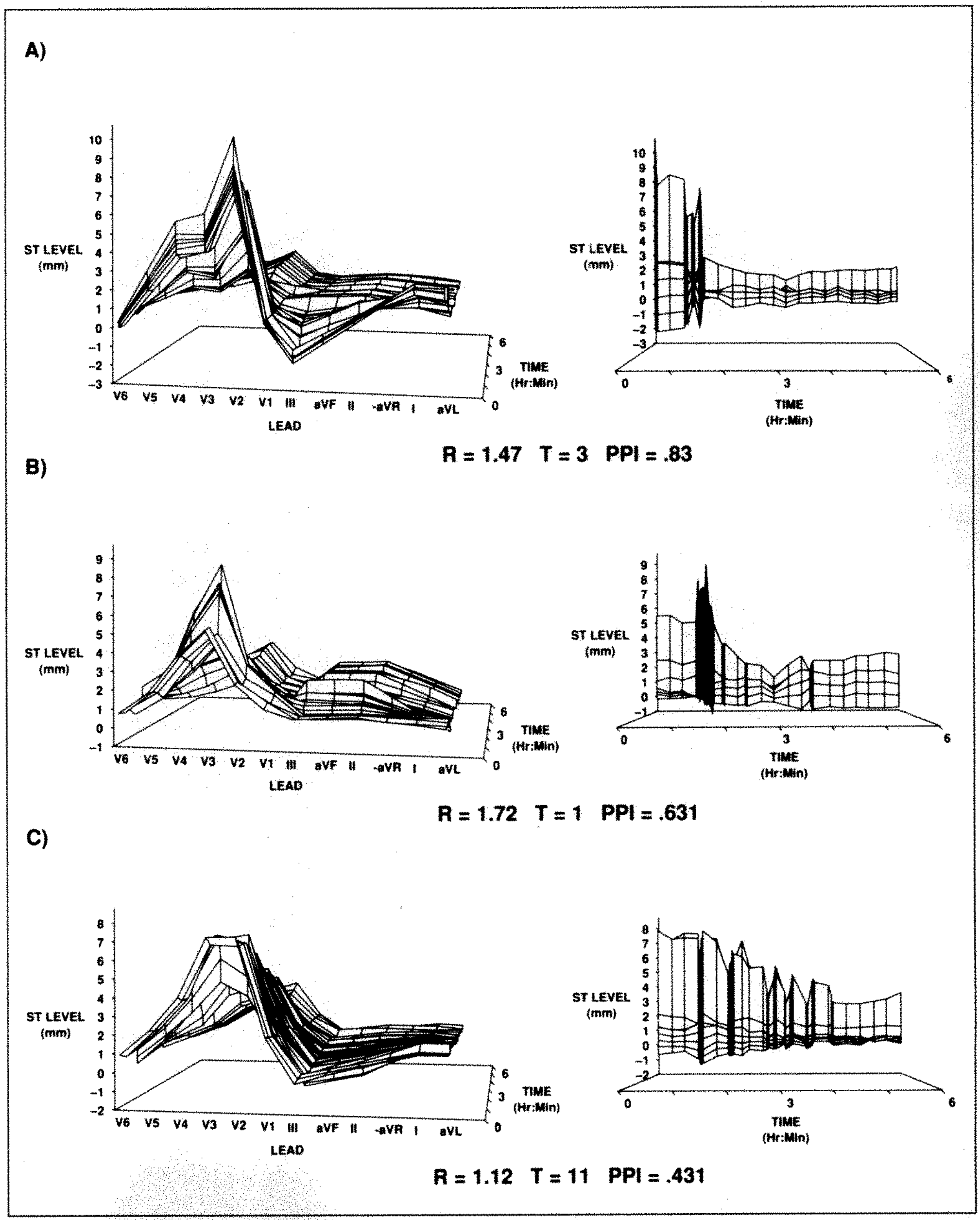

FIGURE 4. ST-monitor data from 3 patients *(A to C)*, all of whom had patent left anterior descending coronary arteries at initial catheterization, shown in same format as Figure 1. Time to first ST-segment recovery (R), the number of transitions (T) and the patent physiology index (PPI) are shown for each patient. See text for discussion.

that cyclic flow changes may not result from therapy, but rather may be the underlying pathophysiology of early infarction on which therapy is superimposed.

It has previously been suggested that cyclic changes in infarct artery patency may have functional importance.[2] Correlations of slow or unstable ST-segment recovery with poor regional wall motion, larger enzymatic infarct size, and poor clinical patient outcome and survival[6,14–17] have been reported. None of these reports, however, have detailed quantitative parameters for cumulative ST recovery over time. The ramifications of such a method are illustrated in Figure 4. In a multifactorial trial design comparing thrombolytic regimens using acute angiographic patency and correlating acute patency to predischarge left ventricular function,[9] all 3 patients in Figure 4 were described as having patent left anterior descending infarct arteries. However, ST-recovery patterns suggest different rates, stability and duration of reperfusion within this "homogenous" angiographic group (Figure 4). The patient in Figure 4A shows early cyclic flow changes and early stable reperfusion. The patient in Figure 4B shows persistent occlusion until just before angiography, with stable reperfusion thereafter. The patient in Figure 4C shows the earliest evidence of reperfusion, but with ongoing cyclic flow changes and very low duration of patency over a 4-hour period before and after angiography. As our pilot data suggest, quantification of cumulative ST recovery over time with parameters reflecting the speed, stability and duration of reperfusion may provide an independent physiologic context for the interpretation of acute angiographic anatomy.

The data we report represent a pilot experience acquired while familiarizing community and university hospitals with the use of 12-lead ST monitors. These data do not represent a prospective or formally blinded analysis, a consecutive patient population, or a sample size large enough to draw rigorous conclusions about the accuracy of the method for real-time patency prediction. Acute angiography was performed by protocol in some and by clinical selection in others. No functional outcome or left ventricular function data were analyzed, so inferences about ST recovery and functional outcome remain unproven.

Despite these limitations, the implications of the method and the pilot results are no less intriguing. Angiographically homogenous subgroups appear to be physiologically heterogenous as quantified by continuous ST-recovery analysis. Seventy-nine percent of our patients with occluded vessels at angiography had at least 1 episode of ST recovery before catheterization, suggesting transient reperfusion. The time to first evidence of reperfusion was somewhat earlier in patients with angiographically occluded vessels than in those with patent arteries. Even our limited data show unequivocally how vulnerable a single angiographic assessment may be to "undersampling" a dynamic phenomenon such as an ongoing myocardial infarction. Determination of the actual additional information content provided by quantification of continuous ST-segment recovery must await a proper prospective trial design in a suitable number of patients. Such research is currently underway.

Serial instantaneous patency assessments based on ST-segment recovery analysis also have clinical management and investigational potential. Current technology makes 12-lead ST-segment monitoring with a portable device feasible in small community hospitals as well as during transport between hospitals, as was frequently done in this pilot. Thus, unlike angiography, ST-segment monitoring can be initiated from the onset of therapy, and can be continued for as long as the patient is at bed rest. Triage of patients given thrombolytic therapy to aggressive or conservative therapeutic strategies could be better studied and managed with a continuous noninvasive marker of failed or unstable reperfusion that was accurate over serial assessments in real time. A prospective, blinded experience including acute catheterization by protocol in a larger patient population is currently being analyzed to better assess the method's performance in this respect.

Thus, this pilot experience demonstrates that continuous 12-lead ST-segment monitoring can be initiated in a timely and practical fashion using currently available technology. Paired with our method of ST-segment recovery analysis using self-referenced, continuously updated measurements, both real time and retrospective determination of the speed and stability of reperfusion appear likely to provide unique and useful information for both investigational and clinical purposes. More rigorous assessment of this potential must await further study.

Acknowledgment: We thank Joseph C. Greenfield, Jr., MD, for his support and guidance in this work and this manuscript, and Ruth G. Wagoner for her invaluable assistance in the final preparation of this paper.

APPENDIX: SUMMARY OF ST-MEASUREMENT AND PARAMETER DEFINITIONS

ST-measurement matrix (trend): (1) the most abnormal single lead from the maximally abnormal electrocardiogram (default), or (2) summated deviation (sum of absolute differences per lead) if either (A) the single most abnormal lead designation changes across ≥2 leads, or (B) there are ≥2 precordial zones show ST elevation.

Transition points: TRANSITION PEAK: the most abnormal electrocardiogram immediately preceding a period of ≥50% ST-segment recovery.

TRANSITION TROUGH: the most normalized electrocardiogram immediately preceding a period of ST reelevation.

ST-segment recovery and reelevation: ST-SEGMENT RECOVERY: (1) resolution of ≥50% of the immediately previous transition peak, or 35 to 49% of the immediately previous transition peak and ≥50% of the most abnormal matrix level over the entire recording period up to the current electrocardiogram, and (2) developing within 3-hour period.

ST-SEGMENT REELEVATION: (1) ST-reelevation developing within a 1-hour period; and (2) lasting >60 seconds; and (3) in matched "fingerprint" zone; and (4) 2 leads ≥150 μV each; or (5) 1 lead ≥200 μV or ≥ST level of immediately previous transition peak, whichever first.

ST-RECOVERY INTERVAL: the time from the first electrocardiogram achieving ST-segment recovery to the time of the first electrocardiogram achieving ST-segment reelevation.

Trend parameters: TIME TO FIRST EVIDENCE OF REPERFUSION: the time from the onset of lytic therapy to the onset of the first ST-segment recovery interval.

PATENT PHYSIOLOGY INDEX PERCENTAGE (PPI%): the sum of the duration of all ST-recovery intervals divided by the duration of the total recording period ×100.

NUMBER OF TRANSITIONS: the total number of transition peaks and troughs over the recording period.

REFERENCES

1. Davies GJ, Chierchia S, Maseri A. Prevention of myocardial infarction by very early treatment with intracoronary streptokinase. *N Engl J Med* 1984; 311:1488–1492.

2. Hackett D, Davies G, Chierchia S, Maseri A. Intermittent coronary occlusion in acute myocardial infarction: value of combined thrombolytic and vasodilator therapy. *N Engl J Med* 1987;317:1055–1059.

3. Krucoff MW, Wagner NB, Pope JE, Mortara DM, Jackson YR, Bottner RK, Wagner GS, Kent KM. The portable programmable microprocessor-driven real-time 12-lead electrocardiographic monitor: a preliminary report of a new device for the noninvasive detection of successful reperfusion or silent coronary reocclusion. *Am J Cardiol* 1990;65:143–148.

4. Krucoff MW. Electrocardiographic Monitoring and Coronary Occlusion: Fingerprint pattern analysis in dimensions of space, time, and mind. Reprint from: *J Electrocardiol* 1989;22:232–237.

5. Kwon K, Freedman B, Wilcox I, Allman K, Madden A, Carter GS, Harris PJ. The unstable ST segment early after thrombolysis for acute infarction and its usefulness as a marker of recurrent coronary occlusion. *Am J Cardiol* 1991;67:109–115.

6. Dellborg M, Riha M, Swedberg K. Dynamic QRS-complex and ST-segment monitoring in acute myocardial infarction during recombinant tissue-type plasminogen activator therapy. *Am J Cardiol* 1991;67:343–349.

7. Dellborg M, Topol EJ, Swedberg K. Dynamic QRS complex and ST segment vectorcardiographic monitoring can identify vessel patency in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 1991; 122:943–948.

8. Krucoff WM, Croll MA, Pendley LP, Burdette DL, Pope JE, Hutchinson DD, Stone JS, Weber RA, Califf RM. Continuous computer-assisted electrocardiographic monitoring in patients with acute myocardial infarction: early experience. *Comput Cardiol* 1989;197–200.

9. Califf RM, Topol EJ, Stack RS, Ellis SG, George BS, Keriakes DJ, Samaha JK, Worley SJ, Anderson Jl, Harrelson-Woodlief L, Wall TC, Phillips HR, Abbottsmith CW, Candela RJ, Wilson DB, Sasahara AA, Mantell S, Lee KL. Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction: the TAMI 5 randomized trial. *Circulation* 1991;83:1543–1556.

10. Pipberger HV, Arzbaecher RC, Berson AS. American Heart Association Committee on Electrocardiography: recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. *Circulation* 1975;52:11–9.

11. Krucoff MW, Green CE, Satler LF, Miller FC, Pallas RS, Kent KM, Del Negro AA, Pearle DL, Fletcher RD, Rackley CE. Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. *Am J Cardiol* 1986;57:916–923.

12. Krucoff MW, Pope JE, Bottner RK, Renzi RH, Wagner GS, Kent KM. Computer-Assisted ST-Segment Monitoring: experience during and after brief coronary occlusion. *J Electrocardiol* 1987;20(suppl):15–21.

13. Krucoff MW, Parente AR, Bottner RK, Renzi Rh, Stark KS, Shugoll RA, Ahmed SW, De Michele J, Stroming SL, Green CE, Rackely CE, Kent KM. Stability of multilead ST-segment "fingerprints" over time after percutaneous transluminal coronary angioplasty and its usefulness in detecting reocclusion. *Am J Cardiol* 1988;61:1232–1237.

14. Krucoff MW, Satler LF, Green CE, Rackley CE, Kent KM. "ST segment changes during early myocardial infarction" In: Califf RM, Wagner GS, eds. Acute Coronary Care 1987. Boston: Martinus Nijhoff, 1987:125–164.

15. Grande P, Hindman NB, Saunamaki K, Prather JD, Hinohara T, Wagner Gl. A comprehensive estimation of acute myocardial infarct size using enzymatic, electrocardiographic and mechanical methods. *Am J Cardiol* 1987;59:1239–1244.

16. Hackworthy Ra, Vogel MB, Harris PJ. Influence of infarct artery patency on the relation between initial St segment elevation and final infarct size. *Br Heart J* 1986;56:222–225.

17. Barbash GI, Roth A, Hod H, Miller HI, Rath S, Har-Zahav Y, Modan M, Seligsohn U, Battler A, Kaplinsky E, Rabinowitz B, Laniado S. Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): results of the Israeli Study of Early Intervention in Myocardial Infarction: *Br Heart J* 1990; 64:241–247.

Frequency and Prognostic Significance of Secondary Ventricular Fibrillation Complicating Acute Myocardial Infarction

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The incidence of secondary ventricular fibrillation (VF) complicating acute myocardial infarction (AMI) was 2.4% in a large cohort of unselected patients with AMI (142 of 5,839). Secondary VF was more frequent in patients with recurrent AMI (4%) than in those with a first AMI (1.9%) ($p < 0.01$). The hospital course was more complicated and in-hospital mortality was significantly higher in patients with secondary VF than in those with the same clinical hemodynamic condition but without VF (56 vs 16%; $p < 0.0001$). Multivariate analyses confirmed secondary VF complicating AMI as an independent predictor of high in-hospital mortality, with an odds ratio of 7 (95% confidence interval 4.6–10.6). However, long-term mortality after discharge (mean follow-up 5.5 years) was not increased in patients with as compared with those without secondary VF (39 vs 42%). These findings were also true when patients receiving β blockers and antiarrhythmic therapy were excluded from analysis. Thus, this life-threatening arrhythmia occurring during hospitalization is not a marker of recurrent susceptibility to VF or an indicator of increased mortality after discharge from the hospital.

(Am J Cardiol 1993;71:152–156)

We recently reported that ventricular fibrillation (VF) in patients without congestive heart failure (primary VF) complicating acute myocardial infarction (AMI) was associated with higher in-hospital mortality, but did not affect the long-term prognosis of hospital survivors of AMI.[1] The data were in accordance with the conclusions of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) study group[2,3] who also reported that secondary VF (VF in the setting of congestive heart failure), although associated with increased in-hospital mortality, did not have a predictive value for survival 1 year after discharge.[4] However, these studies did not specifically assess the possible effect of therapy on the potential value of VF as a marker of risk of subsequent death in patients surviving AMI.

The present study evaluates the incidence of secondary VF, in-hospital characteristics and long-term outcome of patients with secondary VF complicating AMI in a large, nationwide cohort of 5,839 unselected patients hospitalized in 13 coronary care units in Israel.

METHODS

Between 1981 and 1983, we conducted a secondary prevention study entitled Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT). The study examined the use of nifedipine (30 mg/day) versus placebo among 2,276 patients surviving AMI (aged 30 to 74 years) after day 7 of hospitalization. The methods and results were previously reported.[5] Nifedipine did not affect mortality or reinfarction in these patients.[5] During the study period, a log book of all patients with AMI admitted to the coronary care units of the participating hospitals was maintained (SPRINT Registry; n = 5,839).

The study criteria for the diagnosis of AMI were previously published.[6] The Minnesota Code was used for the localization of AMI to anterior (V_1–V_5), inferior (leads 2 and 3, and aVF), lateral (lead 1, aVL and V_6) and undetermined sites.[7]

Continuous electrocardiographic monitoring was performed during the patient's stay (≥48 hours) in the coronary care unit. Cases of VF documented on the bedside monitor, the central monitoring station or by standard electrocardiograph were included in the analysis.

Secondary VF was defined as an occurrence of this arrhythmia in patients in Killip class II or III at the time of the arrhythmia manifestation. Patients in cardiogenic

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*See Appendix.

shock who had VF were excluded from the analysis, because in these cases, VF was "terminal" rather than secondary, with a very high mortality rate (96%) unaffected by the presence of VF. All patients in the same clinical hemodynamic state (Killip class II or III) either on admission or during hospitalization, but without this arrhythmia, constituted the reference group ($n = 1,739$). There was no standard policy of prophylaxis with lidocaine during the study period.

Data acquisition: Demographic, historical and clinical data during hospitalization were collected on study forms for all patients in the Registry. One-year morbidity and mortality follow-up was completed by periodic medical visits, hospital records and, in a small group of patients, telephone interviews. Mortality follow-up was extended to mid-1988 (mean 5.5 years) for 99% of hospital survivors through use of the Israel National Population Registry. All deaths were reviewed independently by 2 cardiologists for assessment of the mode of death and divided into the following 3 main groups: (1) sudden cardiac death (occurring within 24 hours from onset of symptoms), (2) nonsudden cardiac death, and (3) noncardiac death.

Statistical analysis: Age-adjusted prevalence rates of characteristics correlated with secondary VF have been calculated. Multivariate logistic analysis of hospital and postdischarge mortality yielded estimates of the covariate-adjusted predictive power of secondary VF in early (in-hospital) mortality. SAS software was used, specifically the FREQ[8] and CATMOD[9] procedures.

TABLE I Characteristics of Patients Complicated with Secondary Ventricular Fibrillation

	Secondary VF (n = 142) No. (%)	Reference (n = 1,739) No. (%)	p Value
Men	107 (75)	1,240 (71)	NS
Age (year) (mean ± SD)	65 ± 10	66 ± 10	NS
History			
Myocardial infarction	58 (41)	520 (30)	<0.01
Angina pectoris	74 (56)	889 (53)	NS
Systemic hypertension	64 (48)	706 (42)	NS
Diabetes mellitus	28 (20)	366 (21)	NS
Infarct site			NS
Anterior	70 (49)	958 (55)	
Inferior	47 (33)	514 (30)	
Admission (Killip class)			NS
II	76 (54)	833 (48)	
III	11 (8)	188 (11)	
Chest x-ray			
Cardiomegaly	70 (50)	753 (44)	NS
Pulmonary congestion or edema	88 (62)	1,127 (65)	NS
Complications			
Ventricular tachycardia	62 (44)	329 (19)	<0.001
Paroxysmal atrial fibrillation	39 (27)	382 (22)	NS
2° or 3° atrioventricular block	32 (23)	191 (11)	<0.001
Congestive heart failure	98 (69)	945 (54)	0.001
Cardiac enzymes >4/normal			
Creatine kinase	94 (74)	976 (59)	<0.001
Glutamic oxalotransaminase	79 (62)	861 (51)	<0.02
Lactic dehydrogenase	45 (36)	339 (20)	<0.001

VF = ventricular fibrillation.

TABLE II Hospital and Long-Term Mortality in Patients With and Without Secondary Ventricular Fibrillation

	Secondary VF	Reference Group	
	No. (%)	No. (%)	p Value
Hospital	80/142 (56)	271/1,739 (16)	<0.0001
Postdischarge			
1 year	8/62 (13)	244/1,468 (17)	NS
5 years	24/62 (39)	623/1,468 (42)	NS

VF = ventricular fibrillation.

RESULTS

One hundred forty-two of 5,839 patients (2.4%) in the Registry had secondary VF, as defined previously. This incidence was equal in both sexes, and not significantly different in elderly patients and patients with prior angina or systemic hypertension. However, secondary VF was significantly more frequent in patients with a recurrent AMI than in those with a first AMI ($p < 0.001$). Table I summarizes the baseline characteristics and hospital course of patients with and without secondary VF. The group with secondary VF did not differ demographically or by history from the reference group, except for history of AMI, which was significantly higher in the former group. Patients with secondary VF had the same degree of congestive heart failure on admission, but subsequently had a significantly increased rate of congestive heart failure, as well as rhythm disturbances. They had high elevation (>4 times the upper normal limits) of serum cardiac enzymes levels significantly more often than did patients without secondary VF.

The in-hospital mortality rate was 3.5 times higher in patients with secondary VF than in those in the reference group ($p < 0.0001$) (Table II). However, in successfully resuscitated patients during the acute phase, mortality after discharge was not increased (Table II). When mortality after discharge was assessed in hospital survivors who did not receive β blockers or antiarrhythmic drugs on discharge from the hospital, patients successfully resuscitated from secondary VF had similar 1-year (19%) and decreased 5-year (33%) mortality rates compared with those without secondary VF (18 and 45%, respectively), although these differences were not statistically significant. In hospital survivors with anterior AMI, 1- and 5-year mortality were not increased in patients who had secondary VF during hospitalization compared with those without secondary VF (12 and 44% vs 17 and 40%, respectively). In survivors of inferior AMI and secondary VF, 15 and 37% died in 1 and 5 years, respectively, compared with 14 and 40%, respectively, in patients without secondary VF. The causes of hospital and 1-year deaths are presented in Table III. During hospitalization, sudden death was more frequent in patients with (50%) than in those without (41%) secondary VF, but this difference was not statistically significant. The actuarial survival curves of patients with and without secondary VF are shown in Figure 1.

The independence of the association between the occurrence of secondary VF and increased in-hospital mortality was examined by multiple logistic functions within the SPRINT Registry population ($n = 5,839$). After adjustment for age, sex, history of AMI, diabetes, site of the AMI, and serum enzymes in excess of 4 times

TABLE III Mode of Death

	Hospital		After Discharge	
	Secondary VF (n = 80)* No. (%)	Reference (n = 271) No. (%)	Secondary VF (n = 8)† No. (%)	Reference (n = 244) No. (%)
Sudden	40 (50)	110 (41)	3 (37)	114 (47)
Cardiac nonsudden	39 (49)	145 (54)	5 (63)	90 (37)
Other	1 (1)	16 (6)	0 (0)	40 (16)

*p ≤0.06 for difference versus distribution of mode of death in reference group.
†p = NS for difference versus distribution of mode of death in reference group.
VF = ventricular fibrillation.

the upper normal limit, the odds ratio for in-hospital mortality of secondary VF was 7 (95% confidence interval [CI] 4.6–10.6). When, in addition, adjustment was performed for major complications occurring during hospitalization and predictive of hospital mortality, such as 2nd or 3rd degree atrioventricular block, congestive heart failure and prolonged hypotension, the odds ratio of secondary VF was reduced to 5.1 (95% CI 3.5–7.5).

DISCUSSION

Incidence of secondary ventricular fibrillation: The 2.4% incidence of secondary VF complicating AMI in this study (conducted before the introduction of thrombolytic therapy) is lower than that reported in previous studies (4 to 7%),[10,11] but similar to that of the GISSI study (2.7%).[4] Moreover, if patients in cardiogenic shock who had VF were included in our analysis, the incidence of secondary VF would have increased to 3.8% (data not shown). In this study, VF occurring in patients with cardiogenic shock was considered as a "prelethal" arrhythmia, having no additional influence on prognosis, and therefore was excluded from analysis. In the GISSI study[4] the salutary effect of thrombolysis in reducing the incidence of secondary VF was present in patients with congestive heart failure, but not those already in cardiogenic shock. The incidence of secondary VF in the present study was significantly higher in patients with recurrent AMI, but was not affected by gender and age, as previously reported.[4,12] Whereas the higher incidence of secondary VF is in accordance with the greater likelihood of multivessel coronary artery disease or left ventricular dysfunction in patients with recurrent AMI,[12,13] the equal incidence of secondary VF among men and women in this and previous studies is surprising in view of the greater prevalence of adverse baseline factors and higher mortality rates in women during AMI.[4,14]

In-hospital mortality: We found that secondary VF complicating AMI was strongly associated with increased in-hospital mortality. Fifty-six percent of patients in Killip class II or III died in the hospital after VF. The death rate of a large reference group with similarly distributed baseline characteristics and similar clinical severity of AMI on admission to coronary care units was only 16%. The negative prognosis of secondary VF remained after multivariate analysis, including predictors for increased in-hospital mortality, such as history of AMI, higher rate of subsequent congestive heart failure during hospitalization, higher incidence of ventricular tachycardia, advanced atrioventricular block and higher serum enzyme levels (glutamic oxalotransaminase and lactate dehydrogenase), yielding a covariate-adjusted odds ratio of 7 (95% CI 4.6–10.6). Our data on short-term outcome are in accordance with those of previous studies, including GISSI.[4,10,11,15] The significantly increased mortality associated with secondary VF in the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study[11] remained after adjustment for left ventricular ejection fraction.

Whether secondary VF contributes directly to the increase of in-hospital mortality or identifies patients with AMI at higher mortality risk cannot be concluded with certainty from our observations or those of other investigators. Secondary VF may induce sudden hemodynamic deterioration, leading to increased mortality. In several studies, the prophylactic administration of lido-

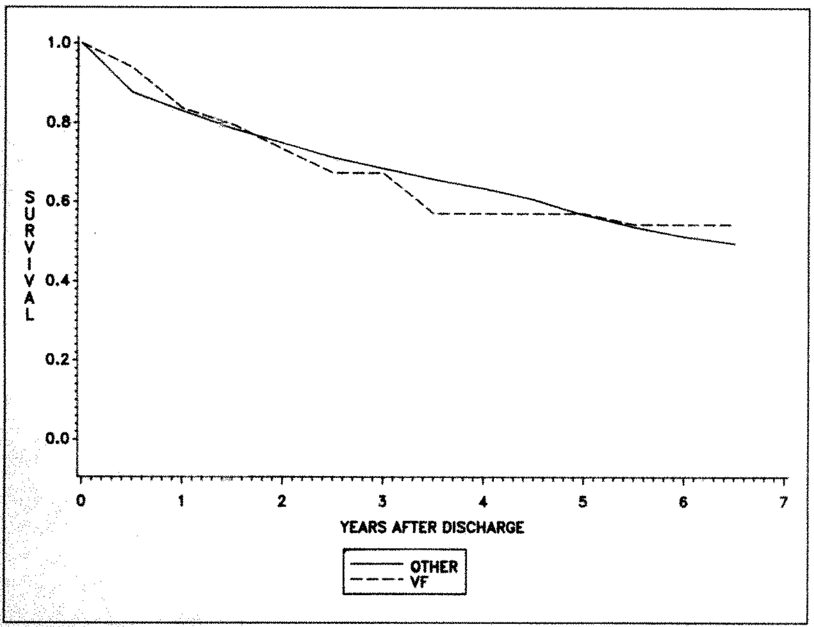

FIGURE 1. Actuarial survival curves of patients with secondary ventricular fibrillation (VF) in comparison with reference group.

caine in AMI, although successful in reducing the incidence of VF, did not produce a substantial reduction of the in-hospital mortality rate.[16–18] The high rate of complications during hospitalization and the increased levels of serum cardiac enzymes in patients with secondary VF suggest that the latter patients may have larger infarcts and therefore are at increased risk.

Long-term mortality: Among patients surviving AMI, the 1-year postdischarge mortality rate was 13% in those resuscitated from secondary VF compared with 17% in those without VF (Table II). These rates were 10.4 and 13.9%, respectively, in the GISSI study.[4]

In a recent study by Schwartz et al,[19] young patients (aged <65 years) with a first anterior AMI, who were successfully resuscitated during hospitalization from ventricular tachycardia or VF, subsequently had significantly reduced mortality if randomized to oxprenolol (2.7%) or to left cardiac sympathetic denervation (3.6%) compared with those allocated to placebo (21.3%) over a mean follow-up of 22 months. In our study, only 11% of surviving patients successfully resuscitated from secondary VF received β blockers, but that treatment was not associated with a reduced mortality. When long-term mortality statistics were compared by AMI site, patients with anterior and inferior AMI had similar mortality rates irrespective of the presence of secondary VF during hospitalization. Most surviving patients after secondary VF in our study were receiving antiarrhythmic drugs that were recently shown not to improve long-term prognosis.[20] No differences in mortality rates were observed between surviving patients with and without secondary VF (39 vs 42%), as found in previous studies with shorter follow-up, suggesting that long-term survival after AMI is not related to the in-hospital occurrence of VF, but to the degree of myocardial damage and extent of coronary artery disease.[21]

In conclusion, this and previous studies[3,4,11] indicate that arrhythmias occurring during hospitalization do not increase the risk of subsequent death in patients surviving AMI.

Acknowledgment: We are most grateful to Mark Goldberg, Dalia Ben-David, Valentina Boyko and Michal Benderly for careful programming and editing of the SPRINT Registry data base, and to Lori Mandelzweig and Lynn Goodman for technical assistance in preparing the manuscript. Mitchell Snyder, PhD, facilitated the use of the SAS CATMOD and NIH procedures for calculating estimates of relative odds, and sensitivity and specificity of the logistic function in discriminating cases from noncases.

APPENDIX

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REFERENCES

1. Behar S, Goldbourt U, Reicher-Reiss H, Kaplinsky E, and the Principal Investigators of the SPRINT Study. Prognosis of acute myocardial infarction complicated by primary ventricular fibrillation. *Am J Cardiol* 1990;66:1208–1211.

2. Volpi A, Maggioni A, Franzosi MG, Pampallona S, Mauri F, Tognoni G. In-hospital prognosis of patients with acute myocardial infarction complicated by primary ventricular fibrillation. *N Engl J Med* 1987;317:257–261.

3. Volpi A, Cavalli A, Franzosi MG, Maggiani A, Mauri F, Santoro E, Tognoni G. One-year prognosis of primary ventricular fibrillation complicating acute myocardial infarction. *Am J Cardiol* 1989;63:1174–1178.

4. Volpi A, Cavalli A, Santoro E, Tognoni G, and GISSI Investigators. Incidence and prognosis of secondary ventricular fibrillation in acute myocardial infarction. *Circulation* 1990;82:1279–1288.

5. The Israeli SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT). A randomized intervention trial of nifedipine in patients with acute myocardial infarction. *Eur Heart J* 1988;9:354–364.

6. SPRINT Study Group. Methodology Manual—SPRINT-1, Coordinating Center, Heart Institute, Sheba Medical Center, Tel Hashomer, July 1981.

7. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Standards and Procedures for Measurement and Classification. Bristol, UK: John Wright, PSG Inc., 1982.

8. The FREQ Procedure. SAS User's Guide: Statistics. Version 5 Edition, Cary, North Carolina: SAS Institute, 1985:403–432.

9. The CATMOD Procedure. SAS User's Guide: Statistics. Version 5 Edition. Cary, North Carolina: SAS Institute, 1985:171–203.

10. Hulting J. Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring. *Acta Med Scand* 1979;206:177–188.

11. Tofler GH, Stone PH, Muller JE, Rutherford JD, Willich SN, Gustafson NF, Poole WK, Sobel BE, Willerson JT, Robertson T, Passamani E, Braunwald E, and the MILIS Study Group. Prognosis after cardiac arrest due to ventricular tachycardia or ventricular fibrillation associated with acute myocardial infarction (the MILIS study). *Am J Cardiol* 1987;60:755–761.

12. Lawrie DM, Higgins MR, Godman MJ, Oliver MF, Julian DG, Donald KW. Ventricular fibrillation complicating acute myocardial infarction. *Lancet* 1968; 2:523–528.

13. O'Doherty M, Tayler DI, Quinn E, Vincent R, Chamberlain DA. Five hundred patients with myocardial infarction monitored within one hour of symptoms. *Br Med J* 1983;286:1405–1408.

14. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S, and the Israeli SPRINT Investigators. In-hospital and 1-year mortality in 1,524 women after myocardial infarction: comparison with 4,315 men. *Circulation* 1991;83:484–491.

15. Dubois Ch, Smeets JP, Demoulin JCl, Pierard L, Foidart G, Henrard L, Tulippe Ch, Presten L, Carlier J, Kulbertus HE. Incidence, clinical significance and prognosis of ventricular fibrillation in the early phase of myocardial infarction. *Eur Heart J* 1986;7:945–951.

16. Lie KI, Wellens HJ, Van Capelli FJ. Lidocaine in the prevention of primary ventricular fibrillation. A double-blind randomized study of 212 patients. *N Engl J Med* 1974;291:1324–1326.

17. Dunn HM, McComb JM, Kinney CD, Campbell NPS, Shanks RG, MacKenzie G, Adgey AAJ. Prophylactic lidocaine in the early phase of suspected myocardial infarction. *Am Heart J* 1985;110:353–362.

18. May GS, Furberg CD, Eberlein KA, Geraci BJ. Secondary prevention after myocardial infarction. A review of short-term acute phase trials. *Prog Cardiovasc Dis* 1983;25:335–359.

19. Schwartz PJ, Motolese M, Pollavini G, Lotto A, Ruberti U, Trazzi R, Bartorelli C, Zanchetti A, and the Italian Sudden Death Prevention Group. Prevention of sudden cardiac death after a first myocardial infarction by pharmacologic or surgical antiadrenergic interventions. *JCE* 1992;3:2–16.

20. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect on encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–412.

21. Califf RM, McKinnis RA, Burks J, Lee KL, Harrell FE, Behar VS, Pryor DB, Wagner GS, Rosati RA. Prognostic implications of ventricular arrhythmias during 24-hour ambulatory monitoring in patients undergoing cardiac catheterization for coronary artery disease. *Am J Cardiol* 1982;50:23–31.

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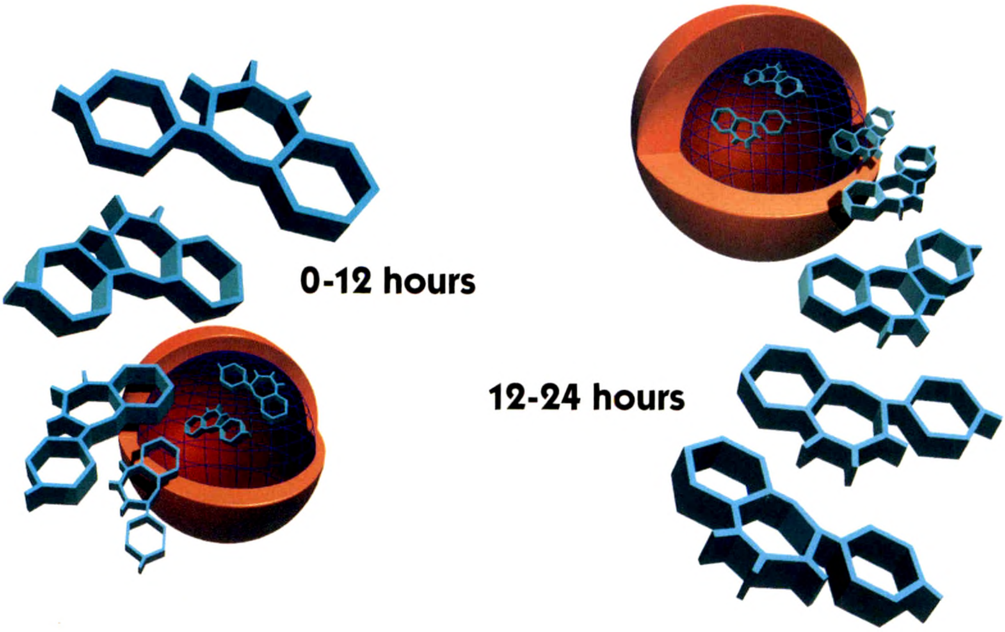
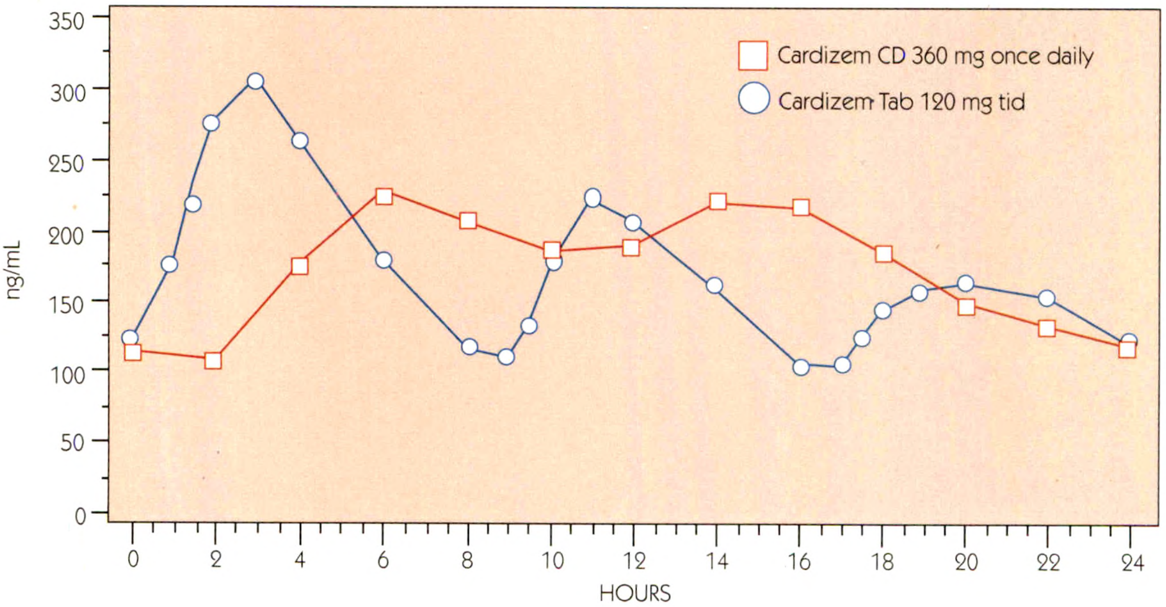


CARDIZEM CD provides 24-hour plasma levels similar to those of Cardizem tablets tid at steady state[1]



One daily dose provides effective plasma levels[1]

* Cardizem CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications. Cardizem CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

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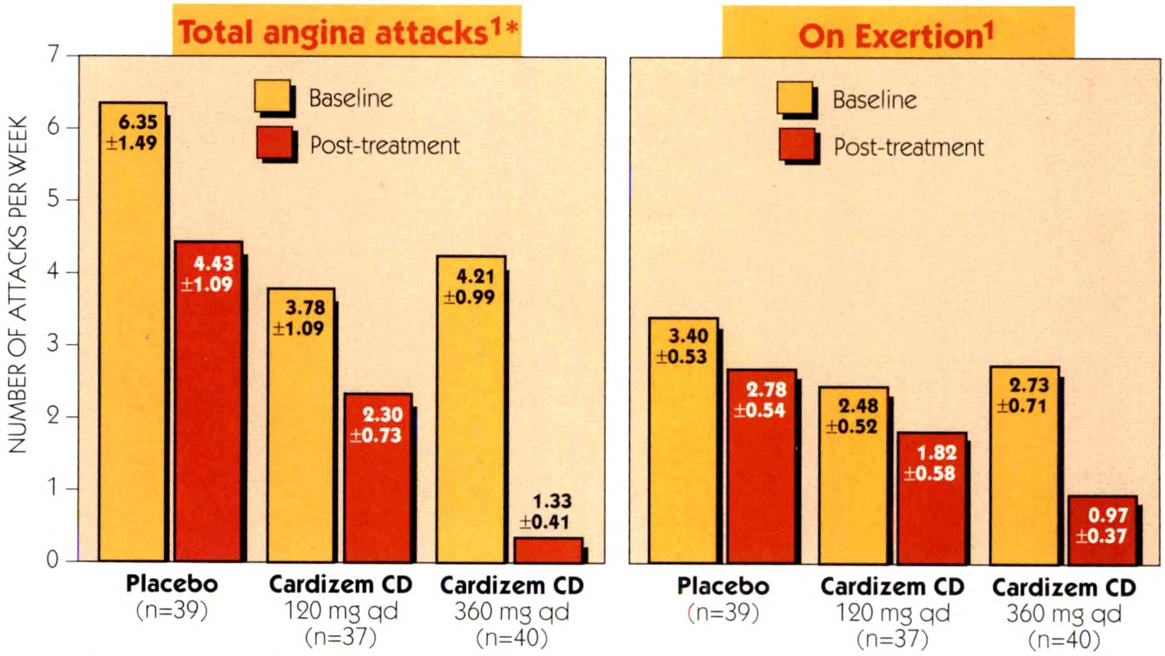
IN ANGINA

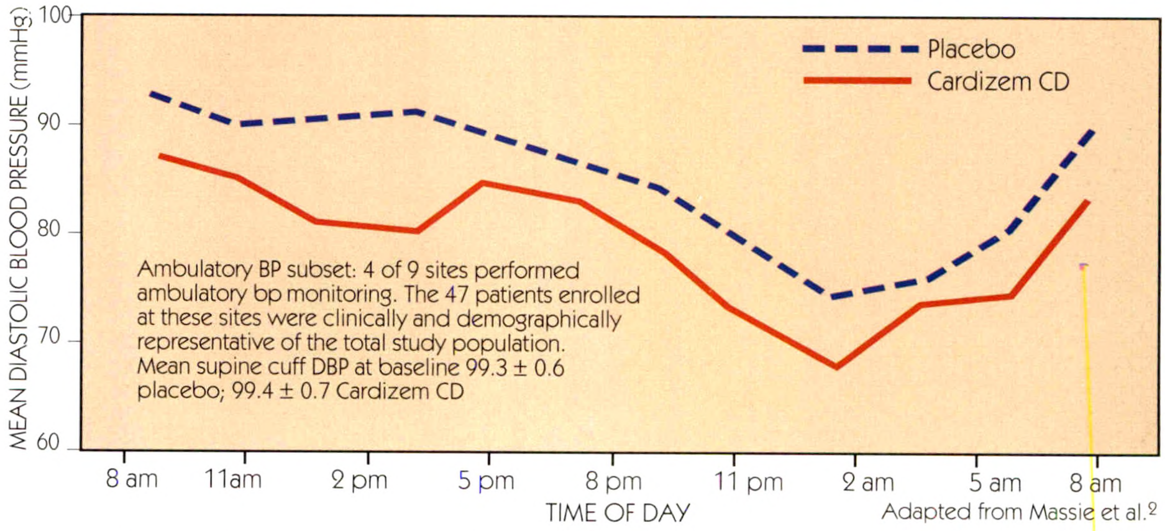
Reduces the frequency of angina attacks —through 24 hours[1]



* At rest and on exertion.

IN HYPERTENSION

Consistent antihypertensive effect seen throughout 24 hours[2]



Ambulatory BP subset: 4 of 9 sites performed ambulatory bp monitoring. The 47 patients enrolled at these sites were clinically and demographically representative of the total study population. Mean supine cuff DBP at baseline 99.3 ± 0.6 placebo; 99.4 ± 0.7 Cardizem CD

Adapted from Massie et al.[2]

- Overall study results (127 patients) show a significant mean change at 24 hours in both diastolic ($P=0.0075$) and systolic ($P=0.0009$) blood pressure vs placebo[2]
- Cardizem CD average daily dose 268 mg/day

Unlike some once-a-day antihypertensives, titration to bid dosing is not necessary with Cardizem CD

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Extremely well tolerated[3]

CARDIZEM CD Placebo-Controlled
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Adverse Reaction	Cardizem CD n=607	Placebo n=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of Cardizem CD capsules, Cardizem tablets, and Cardizem SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

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For angina or hypertensive patients, a recommended starting dose:

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ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

24-HOUR CONTROL OF ANGINA AND HYPERTENSION

Brief Summary of
Prescribing Information as of October 1992 (2)

CARDIZEM® CD
(diltiazem HCl)
Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General.

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions.

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility.

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy.

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled
Angina and Hypertension Trials Combined

Adverse Reaction	CARDIZEM CD N=607	Placebo N=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported.

However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of October 1992 (2)

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb1092(2)a

Available as Once-A-Day

120-mg capsules

180-mg capsules

240-mg capsules

300-mg capsules

Rx
Cardizem CD
Start with one
180-mg
capsule daily

References: 1. Data on file, Marion Merrell Dow Inc. **2.** Massie BM, Der E, Herman TS, Topolski P, Park GD, Stewart WH. *Clin Cardiol.* 1992;15:365-368. **3.** Cardizem CD prescribing information. **4.** *Red Book Update.* 1992;11(10): 7.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
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Comparison of Thrombolytic Therapy for Acute Myocardial Infarction in Patients Aged <35 and >55 Years

Lalit Chouhan, MD, Hajar A. Hajar, MD, and Juan Carlos Pomposiello, MD

There are differences in the risk factor profile and coronary anatomy of young patients who develop coronary artery disease compared with those of older ones. There is an absence of data in published reports regarding the response to thrombolytic therapy and the outcome of acute myocardial infarction in young patients. Sixty-two patients aged <35 years (group 1) were compared with 58 aged >55 years (group 2) who presented with acute myocardial infarction and were treated with intravenous streptokinase.

Group 1 had a significantly higher incidence of smoking (p = 0.0009) and a lower incidence of diabetes mellitus (p = 0.002) than did group 2. Fifty-eight patients in group 1 and 40 in group 2 were studied by angiography at a similar time (5 to 6 days) after admission. Patients in group 1 had a better left ventricular ejection fraction (55 ± 13% vs 49 ± 13%; p = 0.03), but similar patency rates of the infarct vessel (74 vs 73%) compared with those of group 2. Group 1 also had a higher incidence of insignificant disease (22.5 vs 2.5%; p = 0.008) and a lower incidence of 3-vessel disease (10 vs 37.5%; p = 0.004). This suggests that there are differences in the risk factor profiles and coronary anatomy of young patients compared with those of older ones. Despite similar benefits from thrombolytic therapy in the form of a patent infarct vessel, there may be differences in the long-term outcome among these patients.

(Am J Cardiol 1993;71:157–159)

Although coronary artery disease in young patients is not as frequent as in elderly ones, there is growing awareness of its existence in the young. It has been shown that there are differences in the risk factor profile and hospital mortality of young patients with acute myocardial infarction compared with those of older ones.[1] Coronary angiography in young patients with coronary artery disease shows a preponderance of 1-vessel disease, and a significant portion also show no significant coronary artery disease.[2] There is an absence of data in published reports regarding thrombolytic therapy for acute myocardial infarction in the young. The purpose of this study was to examine the clinical and angiographic features of young patients (aged <35 years) who were treated with intravenous streptokinase for acute myocardial infarction and compare them with those of older ones (aged >55 years).

METHODS

Patient population: All patients treated with intravenous streptokinase for acute myocardial infarction at the Hamad General Hospital between January 1987 and December 1990 who were aged <35 or >55 years were analyzed for this study. All patients had subsequent confirmation of acute myocardial infarction by increased creatine kinase and its MB isoenzyme.

Criteria for streptokinase treatment included the following: (1) typical acute chest pain lasting >30 minutes, unrelieved by nitroglycerin; (2) ST-segment elevation >1 mm in 2 contiguous leads; (3) total duration of symptoms <6 hours; and (4) age <70 years. Patients were excluded from the study if they had: (1) history of allergy to streptokinase or of receiving streptokinase in the previous 6 months, (2) history of cerebrovascular accident, (3) major neurologic, thoracic, abdominal or vascular surgery in the past month, (4) cardiac massage during admission for acute myocardial infarction, (5) severe anemia, bleeding or coagulation abnormality, (6) incurable primary disease (e.g., cancer), or (7) uncontrolled hypertension (systolic pressure >200 mm Hg, and diastolic pressure >110 mm Hg).

Treatment regimen: Streptokinase in a dose of 1.2 to 1.5 million units was infused intravenously over 40 minutes. Heparin was initiated after completion of streptokinase infusion at 1,000 units/hour and was adjusted subsequently by checking the partial thromboplastin time to maintain it at 1.5 to 2.0 times the control value. Heparin was usually continued for 5 days after acute myocardial infarction. Other drugs such as nitrates, β

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TABLE I Clinical Characteristics of Patients

	Group 1	Group 2	p Value
No.	62	58	
Age (year)	33 ± 3	60 ± 5	<0.0001
Men/women	61/1	54/4	NS
Serum cholesterol (mg/dl)	211 ± 50	228 ± 46	0.07
Hypercholesterolemia (%)	40	53	NS
Diabetes mellitus (%)	11	36	0.002
Systemic hypertension (%)	10	9	NS
Cigarette smoking (%)	77	47	0.0009
Family history	15	5	NS
No. of risk factors	1.5 ± 1.0	1.48 ± 0.86	NS
Patients with ≥ 1 risk factor (%)	89	88	NS
Time from pain to SK (min)	193 ± 176	190 ± 103	NS
Site of infarct (%)			
Anterior	68	60	NS
Inferior	32	29	NS
Undetermined	0	11	NS

SK = streptokinase.

blockers, calcium antagonists and aspirin were used as needed.

Catheterization studies: Left heart catheterization with coronary angiography was performed in patients at an average of 5.16 ± 2.88 days after the onset of symptoms. Baseline ventricular end-diastolic pressure was measured in all patients. Left ventricular ejection fraction was calculated by the area length method on all angiograms.[3] A ≥50% luminal narrowing of the left main, left anterior descending, circumflex or right coronary artery was considered to represent coronary artery disease. Multiple sites of significant disease in the same coronary artery or its main branches were considered to represent 1-vessel involvement. Significant disease of the left main artery was considered to represent 2-vessel disease. A combination of information from the electrocardiogram during admission, wall motion abnormalities of the left ventriculogram during angiography, and coronary anatomy was used to determine the infarct-related artery. Patency of the infarct-related artery was determined using Thrombolysis in Myocardial Infarction (TIMI) grade classification.[4] A patent infarct artery was defined as having TIMI grade 2 or 3 anterograde flow. An artery with TIMI grade 0 or 1 was considered to be occluded. Two experienced angiographers independently interpreted the results of the angiograms.

Statistical analysis: All continuous data are expressed as mean ± 1 SD. Chi-square and Fisher's exact test were used for discrete proportions, and Student's *t* test for continuous data. A p value <0.05 was considered statistically significant.

RESULTS

Of 420 patients treated with streptokinase for acute myocardial infarction, 62 were aged <35 years (range 24 to 35; group 1) and 58 were aged >55 years (range 55 to 70; group 2). Baseline clinical characteristics of patients are listed in Table I. Although the prevalence of hypercholesterolemia was comparable in both groups, the level of serum cholesterol in young patients was less than in older ones (211 ± 50 vs 228 ± 46 mg/dl; p = 0.07). Group 1 had a lower incidence of diabetes mellitus (11 vs 36%; p = 0.002) and a higher incidence of smoking (77 vs 47%; p = 0.0009) than did group 2. Most patients in both groups had ≥1 cardiac risk factor, and the total number of risk factors in both groups was comparable. The 3 most frequent cardiac risk factors in young patients were smoking, hypercholesterolemia and family history of coronary artery disease, whereas in older patients these were hypercholesterolemia, smoking and diabetes. The time interval from onset of symptoms to therapy with streptokinase was similar in both groups. Most patients in both groups had anterior infarctions, and the distribution of the site of infarction was similar in both groups.

Angiographic findings (Table II): Fifty-eight patients in group 1 and 40 in group 2 were studied by angiography at a similar time interval from admission. Death before the study (1 in group 1, and 6 in group 2) or refusal were the 2 reasons for not studying the remaining patients. Both groups had similar left ventricular end diastolic pressures, but left ventricular ejection fraction was greater in younger patients (55 ± 13% vs 49 ± 13%; p = 0.03). The patency rates of the infarct vessel in both groups were comparable. Patients in group 1 had a higher incidence of insignificant coronary artery disease (22.5 vs 2.5%; p = 0.008) and a lower incidence of 3-vessel disease (10 vs 37.5%; p = 0.004).

TABLE II Angiographic Findings

	Group 1	Group 2	p Value
Total no.	62	58	
No. studied	58	40	
Time to study (days)	5.9 ± 3.0	6.9 ± 3.7	NS
Left ventricular end-diastolic pressure (mm Hg)	18.70 ± 10.58	17.55 ± 7.38	NS
Left ventricular ejection fraction (%)	55 ± 13	49 ± 13	0.03
Patency of infarct-related artery (%)	74	73	NS
No. of vessels with coronary artery disease	1.21 ± 0.91	2.02 ± 0.88	0.0001
Extent of coronary artery disease			
0 vessel	13 (22.5%)	1 (2.5%)	0.008
1 vessel	26 (45%)	11 (27.5%)	NS
2 vessels	13 (22%)	13 (32.5%)	NS
3 vessels	6 (10%)	15 (37.5%)	0.004
Recommended therapy			
Medical treatment	32 (55%)	24 (60%)	NS
Angioplasty	18 (31%)	6 (15%)	NS
Bypass grafting	8 (14%)	10 (25%)	NS

Based on coronary anatomy, management in the form of medical treatment, coronary angioplasty or coronary artery bypass grafting was recommended (Table II) in both groups.

DISCUSSION

Coronary risk factors in young patients: Several studies have shown that smoking,[1,5–8] high cholesterol[2,7,8] and family history of coronary artery disease[1,8] are the most frequent risk factors in young patients with coronary artery disease. However, systemic hypertension and diabetes mellitus may not be as prevalent in younger age groups as in older ones.[1,2,5,7–11] It has also been shown that the incidence of prior angina and heart failure was found to increase with age.[11] The present study also confirms some of these observations. It appears that the number of risk factors present has a role in the extent of coronary artery disease.[1,5,10,12] Similar to our experience, previous studies[8,13] showed that most (up to 90 to 97%) young patients with acute myocardial infarction have ≥1 cardiac risk factor. With increasing age, patients were less frequently treated with thrombolytic therapy for acute myocardial infarction, because of a higher incidence of complicating illness, absence of chest pain on admission and nonspecific electrocardiographic abnormalities at presentation.[11]

Angiographic findings: Less extensive coronary artery disease is a well-known finding in young versus older patients.[1,8,10,13] The preponderance of involvement of the left anterior descending artery in young subjects is also well known.[8–10,12] There is an absence of data in published reports regarding comparison of the coronary anatomy in young and old patients after thrombolytic therapy. The present study found equal patency rates in all age groups after therapy with streptokinase for acute myocardial infarction. The residual coronary anatomy appears to follow the distribution reported in the literature (i.e., less extensive 3-vessel disease, and greater proportion of insignificant and 1-vessel disease in the young). The rate of progression of atherosclerotic coronary disease is faster in young patients than in older ones with medical treatment.[14,15] Follow-up studies of coronary artery bypass graft surgery in young versus old patients have shown greater progress of atherosclerosis in the saphaenous vein grafts of the young.[16–18] Young patients are also more likely to complain of angina at long-term follow-up and to need reoperation.[9] A similar accelerated progress of the disease in native vessels in younger patients has also been shown after coronary angioplasty,[19] necessitating repeat angioplasty in up to 53% of patients.

Study limitation: Not all patients were assessed in this study by angiography, especially in the older group, because social factors prevalent in the area make older patients reluctant to undergo invasive procedures.

REFERENCES

1. Uhl GS, Farrel PW. Myocardial infarction in young adults; risk factors and natural history. *Am Heart J* 1983;105:548–553.
2. Bergstrand R, Vedin A, Wilhelmsson C, Waltin J, Wedel H, Wilhelmsen L. Myocardial infarction among men below age 40. *Br Heart J* 1978;40:783–788.
3. Sandler H, Dodge HT. The use of single plane angiocardiogram for the calculation of left ventricular volume in man. *Am Heart J* 1968;75:325–334.
4. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase 1 findings. *J Am Coll Cardiol* 1983;1:1254–1261.
5. Glover MU, Kuber MT, Warren SE, Vieweg WVR. Myocardial infarction before age 36: Risk factor and arteriographic analysis. *Am J Cardiol* 1982;49:1600–1603.
6. Elmfeldt D, Wilhelmsson C, Vedin A, Tibbin G, Wilhelmsen L. Characteristics of representative male survivors of myocardial infarction compared with representative population samples. *Acta Medica Scandinavica* 1976;199:387–398.
7. Dolder MA, Oliver MF. Myocardial infarction in young men. Study of risk factors in nine countries. *Br Heart J* 1975;37:493–503.
8. Nitterhauge S, Erikson J, Thaulow E, Vatne K. Angiographic and risk factor characteristics of subjects with early onset ischemic heart disease. *Br Heart J* 1981;46:325–330.
9. Kelly ME, DeLaria GA, Najafi H. Coronary artery bypass surgery in patients less than 40 years of age. *Chest* 1988;94:1138–1141.
10. Wolfe MW, Vacek JL. Myocardial infarction in the young. Angiographic features and risk factor analysis of patients with myocardial infarction at or before the age of 35 years. *Chest* 1988;94:926–930.
11. Weaver WD, Litwin PE, Martin JS, Kudenchuk PJ, Maynard C, Eisenberg MS, Ho MT, Cobb LA, Kennedy JW, Wirkus MS. The MITI Project Group. *J Am Coll Cardiol* 1991;18:657–662.
12. Van Haecke J, Piessens J, Willems JC, Geest HD. Coronary arterial lesions in young men who survived a first myocardial infarction: clinical and electrocardiographic predictors of multivessel disease. *Am J Cardiol* 1981;47:810–814.
13. Al-Koubaisy OK, Mehdi RS, Arem FD, Ahmed IT. Cineangiographic findings in young Iraqi men with first acute myocardial infarction. *Cathet Cardiovasc Diagn* 1990;19:87–90.
14. Kramer JR, Matsuda Y, Mulligan JC, Aronow M, Proudfit WL. Progression of coronary atherosclerosis. *Circulation* 1981;63:519–526.
15. Marchandise B, Bourassa MG, Chaitman BR, Lesperance J. Angiographic evaluation of the natural history of normal coronary arteries and mild coronary atherosclerosis. *Am J Cardiol* 1978;41:216–220.
16. Lytle BW, Kramer JR, Golding LR, Cosgrove DM, Borsh JA, Goormastic M, Loop FD. Young adults with atherosclerosis: 10 year result of surgical myocardial revascularization. *J Am Coll Cardiol* 1984;4:445–453.
17. Fitzgibbon GM, Hamilton MG, Leach AJ, Kafka HP, Markle HV, Keon WJ. Coronary artery disease and coronary bypass grafting in young men: experience with 138 subjects 39 years of age and younger. *J Am Coll Cardiol* 1987;9:977–988.
18. Radtke HJ, Hahn C, Roskamm H, Schmuziger M. Myocardial revascularization in patients under 40 years of age. In: Roskamm H, ed. Myocardial Infarction at Young Age. New York: Springer Verlag, 1981:201–207.
19. Stone GW, Lizon RW, Rutherford BD, McConahay DR, Hartzler GO. Short-erm outcome and longterm followup following coronary angioplasty in the young patients: a 8 year experience. *Am Heart J* 1989;118:873–877.

Relation of Apolipoprotein E Phenotype to Myocardial Infarction and Mortality from Coronary Artery Disease

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The apolipoprotein E polymorphism is a genetic determinant of low-density lipoprotein (LDL) cholesterol. Its status as a risk factor for coronary artery disease (CAD), either through a causal relation with LDL cholesterol level or independently, is less clearly established. Data from the Multiple Risk Factor Intervention Trial were used to examine the influence of apolipoprotein E phenotype on risk of coronary events. Of the 12,866 randomized participants, 619 were studied in a nested case-control design. CAD deaths (93) and nonfatal myocardial infarctions (113) were matched to 412 controls. The allele frequencies of apolipoprotein E in the white subset ($\epsilon 2 = 0.06$, $\epsilon 3 = 0.79$, and $\epsilon 4 = 0.15$) were very similar to other nonselected white American populations, and the relation of apolipoprotein E on total and LDL cholesterol was generally similar to that seen in other studies, with the ϵ2 allele being associated with lower and the ϵ4 allele with higher total and LDL cholesterol. Allele frequencies were not the same for patients and control subjects. The presence of ϵ4 was associated with an increased risk of CAD that was most evident for fatal cases. There was no relation between changes in LDL cholesterol over time during the trial and apolipoprotein E phenotypes.

(Am J Cardiol 1993;71:160–165)

The apolipoprotein E polymorphism has been shown to be a heritable determinant of total and low-density lipoprotein (LDL) cholesterol. It has been the object of numerous epidemiologic, genetic, biochemical and molecular studies. Epidemiologic studies have provided clear evidence that apolipoprotein E structural variation is a determinant of interindividual differences about the population sample means of total and LDL cholesterol and apolipoprotein B.[1,2] The genetically determined isoforms, E2, E3 and E4, are inherited in a co-dominant fashion following translation of 3 common alleles ϵ2, ϵ3 and ϵ4 at a single genetic locus located on chromosome 19.[3,4] The 6 phenotypes, E 2-2, 3-2, 3-3, 4-3, 4-4 and 4-2, occur with frequencies dependent on the allele frequencies in each population. There are relatively high frequencies for ϵ2 (ϕ 0.07) and ϵ4 (ϕ 0.14) in the American Caucasian population, but the most common allele in all populations studied to date is ϵ3.[1]

In vivo and in vitro investigations of the mechanisms by which the apolipoprotein E polymorphism leads to alterations in lipids and lipoproteins have been carried out.[5–10] Apolipoprotein E modulates the catabolism of triglyceride depleted remnants of chylomicrons and very low density lipoproteins by acting as a ligand for the LDL receptor (B/E receptor) and for the chylomicron remnant receptor. It is also found in high-density lipoprotein (HDL) cholesterol. Decreased LDL cholesterol in carriers of E2 is due to both decreased rates of production and increased rates of catabolism, whereas the opposite is true for E4 carriers.[10,11] A question of current interest is whether apolipoprotein E phenotype is protective (E2 carriers) or increases risk (E4 carriers) for atherosclerosis and coronary artery disease (CAD) based on its respective impact on LDL cholesterol concentrations.[12–18]

In the study of the Pathobiological Determinants of Atherosclerosis in Youth, investigators in 8 communities evaluated 720 young men who had died from external causes.[19] The extent of atherosclerosis in the thoracic and abdominal aorta was greatest in those who were E 4-3 and least in those who were E 3-2. Adjusting for serum cholesterol did not change these associations. The present study is aimed at determining if, and to what extent apolipoprotein E phenotype, is related to CAD death and myocardial infarctions in the Multiple Risk Factor Intervention Trial. The study is unique because of its prospective nature. Lipid and lipoprotein levels, as well as other risk factor levels, were recorded from a baseline screening of men at risk for CAD before developing CAD events.[20,21]

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TABLE I Mean Total Cholesterol, Lipids and Other Coronary Artery Disease Risk Factors at Baseline by Apolipoprotein E Phenotype

	Apolipoprotein E Phenotype				
	3-2 (n = 59)	3-3 (n = 386)	4-3 (n = 146)	4-4 (n = 16)	p Value (3 df)
Total plasma cholesterol (mg/dl)	233	241	244	254	0.13
Low-density lipoprotein cholesterol (mg/dl)	143	163	166	166	<0.001
High-density lipoprotein cholesterol (mg/dl)	41	41	40	42	0.70
Triglycerides (mg/dl)	237	198	192	258	0.11
Age (year)	47	47	47	47	0.99
Body mass index (kg/m^2)	26.8	27.6	28.2	29.1	0.02
Systolic blood pressure (mm Hg)	135	135	135	132	0.83
Diastolic blood pressure (mm Hg)	92	90	90	90	0.59
Albumin (g %)	4.5	4.6	4.5	4.5	0.77
% smokers	73	64	64	56	0.48
Drinks/week	13	12	10	09	0.21

Means for lipids and lipoproteins were adjusted for age, cigarettes, diastolic blood pressure and body mass index.
df = degrees of freedom.

METHODS

Study population: Subjects were male randomized participants to the Multiple Risk Factor Intervention Trial, a national multicenter primary prevention trial aimed at intervening on CAD risk factors in middle-aged men (35 to 57 years). In the original study, 12,866 high-risk men, selected on the basis of their levels of diastolic blood pressure, serum cholesterol and number of cigarettes smoked,[20] were randomized at 22 clinical centers from December 1973 to February 1976 to special intervention [n = 6,428] or usual care [n = 6,438]. Clinical follow-up of the participants ended on February 28, 1982. Since that time, mortality surveillance of the Multiple Risk Factor Intervention Trial participants has continued through December 31, 1985. Mortality results through 10.5 years of follow-up have been reported.[21] Vital status was determined using the National Death Index after February 1982. Mortality ascertainment through December 31, 1985 is estimated to be 100% complete.[21]

The present investigation is a case-control study nested within the randomized study. There were 93 CAD deaths and 114 patients with nonfatal myocardial infarction. Cases of CAD are matched to 412 control subjects by clinical centers, treatment group (special intervention vs usual care), date of randomization within ± 30 days, and age within ± 5 years. Control subjects had not experienced a CAD event before the time of the event experienced by the patient. Each patient was matched to 2 control subjects forming a triad. There were 4 triads (1 CAD death and 3 myocardial infarctions) with only 1 control and 1 myocardial infarction triad in which both control subjects did not have an apolipoprotein E phenotype because serum was not available. Finally, there were 4 control subjects with apolipoprotein E phenotypes but no matched patient.

Serum samples from these 619 study subjects have been frozen since 1975. All deaths occurred after the conclusion of the main study, between 1982 and 1986. Serum samples from men who experienced a CAD death during the course of the trial were not available because they had been used for other studies.[22] CAD deaths were based on information from death certificates, defined as International Classification of Disease codes 410 to 414 and 429.2, based on the Ninth Revision of the International Classification of Disease. Nonfatal myocardial infarctions were ascertained through February 28, 1982 using previously described methods.[23]

Laboratory assays: After the initial screening at which CAD risk eligibility was determined, participants had 2 further examinations before randomization. At the second screening, blood samples were obtained after a 12-hour fast. A plasma sample was used for measurement of total cholesterol, HDL cholesterol and triglycerides. These laboratory measurements were done in a central laboratory at the Institute of Medical Sciences in San Francisco which was carefully monitored by the Centers for Disease Control Lipid Standardization Program. Details of the laboratory methods have been published.[24]

A serum sample from the second screening was frozen for each participant. The sample was used for apolipoprotein E screening in 1990, according to the protocol described by Eichner et al (1990)[25] using isoelectric focusing and immunoblotting of delipidated serum samples. The samples that had been frozen at −60 to −70°C for 14 to 15 years gave very clear phenotypes. The phenotypes were read from the immunoblots, recorded, read again to check the initial typings and read a third time before data were entered in the computer. Phenotypes that were equivocal were repeated. The author (JE) reread 98 of the immunoblots blindly, and there was complete agreement with the previous readings. Because many of the Multiple Risk Factor Intervention Trial participants had elevated lipid levels, and probably elevated apolipoprotein E levels, the phenotypes were especially distinct.[25] The phenotypes used are assumed to reflect genotypes, but no deoxyribonu-

TABLE II Distribution of Apolipoprotein E Phenotypes in Patients with Coronary Artery Disease (CAD) (CAD deaths and nonfatal myocardial infarctions) and in Control Subjects

	CAD Deaths		Nonfatal Myocardial Infarctions		All Patients		Control Subjects	
	No.	%	No.	%	No.	%	No.	%
2-2	1	1.1	0	0	1	0.5	2	0.5
2-variant	1	1.1	0	0	1	0.5	0	0
3-2	8	8.6	16	14	24	11.6	35	8.5
3-3	43	46.2	67	58.8	110	53.1	276	67
4-2	4	4.3	0	0	4	1.9	4	1
4-3	31	33.3	30	26.3	61	29.5	85	20.6
4-4	5	5.4	1	0.9	6	2.9	10	2.4
Total	93	100	114	100	207	100	412	100

TABLE III Summary of Matched Logistic Regression Results for Apolipoprotein E

Apoliprotein E Phenotype	CAD Death (n = 114)		Nonfatal MI (n = 87)		All Triads (n = 201)	
	RR	95% CI	RR	95% CI	RR	95% CI
Univariate Results						
3-3	1.0	—	1.0	—	1.0	—
3-2	1.7	0.6–4.3	1.7	0.8–3.4	1.7	0.97–3.00
4-3	2.0	1.1–3.6	1.5	0.9–2.6	1.7	1.13–2.50
4-4	11.8	1.3–106.5	0.3*	0.0–2.3	1.5	0.51–4.27
Chi-square (3 df)	11.2		5.8		8.6	
p value (3 df)	0.01		0.12		0.04	
Multivariate Results†						
3-3	1.0	—	1.0	—	1.0	—
3-2	1.7	0.6–4.8	1.8	0.9–3.9	1.7	1.0–3.2
4-3	2.3	1.2–4.3	1.5	0.8–2.7	1.8	1.2–2.7
4-4	8.7	0.9–87.3	0.3†	0.0–2.6	1.4	0.4–4.3
Chi-square (3 df)	11.4		5.4		9.1	
p value (3 df)	0.01		0.14		0.03	

*There was only 1 nonfatal myocardial infarction among apolipoprotein E 4-4 patients.
†Adjusted for age, cigarettes/day, diastolic blood pressure, body mass index and low-density lipoprotein cholesterol.
CAD = coronary artery disease; CI = confidence interval; df = degrees of freedom; RR = relative risk.

cleic acid samples were available to confirm this. Gene frequencies were calculated based on scoring of apolipoprotein E gene products.

Statistical analyses: Analysis of covariance was used to assess the relation between phenotype and lipid and lipoprotein levels controlling for age, body mass index, diastolic blood pressure and cigarettes smoked per day.[26] Analysis of variance and chi-square tests were used to compare apolipoprotein E phenotype and other risk factors at baseline.[26] Matched logistic regression was used to assess the relation of phenotype and CAD status.[27] Relative risks were calculated relative to phenotype 3-3. The likelihood ratio statistic with 3 degrees of freedom was used to assess differences in risk among the phenotype groups. For this analysis only phenotypes 3-2, 3-3, 4-3 and 4-4 were used. Two-way analysis of variance with interaction was used to assess whether the effect of various risk factors in CAD differed by apolipoprotein E phenotype.

RESULTS

Table I shows the relation between phenotype and other variables at baseline including lipids and lipoproteins. A significant difference in LDL cholesterol was found between phenotypes ($p < 0.001$) with the E 3-2 group, having a 20 to 23 mg/dl lower mean LDL cholesterol then the other phenotype groups. No significant differences were found for the other lipids, although the E 3-2 group had lower total cholesterol and higher triglycerides then the 3-3 and 4-3 phenotype groups. Other differences between groups at baseline were found only for body mass index.

Table II gives the distribution of apolipoprotein E phenotypes in patients (separated into CAD deaths and nonfatal myocardial infarctions) and control subjects. Patients had a higher percentage of apolipoprotein E phenotype 4-3 and a smaller percentage of E 3-3 than control subjects (chi-square based on 4 phenotype classes = 10.3, 3 degrees of freedom, $p = 0.02$). The difference between patients and control subjects was greater in the CAD death group.

Table III lists the results of the matched logistic regression analyses relating apolipoprotein E phenotypes to CAD status. There were significant differences in CAD risk among the phenotypes univariately ($p = 0.04$) and after adjusting for age, cigarettes per day, diastolic blood pressure, body mass index and LDL cholesterol ($p = 0.03$) with the phenotype groups 3-2, 4-3 and 4-4 having similar increased risks (1.5 to 1.7) compared with phenotype group 3-3. The increased risk for the 3-2 group compared with the 3-3 group was similar for CAD deaths and nonfatal myocardial infarctions, with higher risks in the CAD

TABLE IV Mean Change in Low-Density Lipoprotein Cholesterol (±SE) at Six Years for Four Apolipoprotein E Phenotypes in Patients (coronary artery disease deaths and nonfatal myocardial infarctions) Compared with Control Subjects

	Apolipoprotein E 3-2	Apolipoprotein E 3-3	Apolipoprotein E 4-3	Apolipoprotein E 4-4	p Value (3 df)
CAD deaths	−11.0 (.84) (n = 8)	−5.4 (4.9) (n = 37)	−7.6 (5.4) (n = 27)	−14.8 (13.0) (n = 4)	0.90
Nonfatal myocardial infarctions	−15.2 (98) (n = 12)	−14.8 (3.2) (n = 62)	−22.2 (5.1) (n = 25)	—	0.69
Control subjects	−6.7 (5.7) (n = 30)	−7.5 (1.8) (n = 247)	−9.6 (3.4) (n = 76)	14.9 (7.8) (n = 9)	0.11
p value (2 df)	0.72	0.14	0.11	0.06	

CAD = coronary artery disease; df = degrees of freedom.

TABLE V Comparison of Risk Factors for Patients with Coronary Artery Disease (CAD) (myocardial infarction and CAD death) and in Control Subjects by Apolipoprotein E Phenotype

	Apolipoprotein E Phenotype									
	2-2, 3-2			3-3			4-3, 4-4			
	Pts.	Control Subjects	p Value	Pts.	Control Subjects	p Value	Cases	Control Subjects	p Value	p Value Interaction*
No. of participants	25	37		109	270		67	94		
Total cholesterol (mg/dl)	235	231	0.73	247	238	0.03	249	243	0.33	0.84
Triglycerides (mg/dl)	244	237	0.87	230	183	0.01	186	214	0.18	0.05
LDL cholesterol (mg/dl)	143	138	0.60	164	162	0.64	172	161	0.06	0.39
HDL cholesterol (mg/dl)	40	42	0.40	40	42	0.09	39	40	0.80	0.71
Systolic blood pressure (mm Hg)	137	133	0.35	138	134	0.01	134	135	0.74	0.19
Diastolic blood pressure (mm Hg)	92	92	0.92	92	90	0.04	90	90	0.81	0.32
Cigarettes/day	28	21	0.14	27	21	0.01	27	19	0.02	0.95
Age (year)	48	46	0.30	47	47	0.99	47	47	0.67	0.61

*Interaction is between the apolipoprotein E phenotype and the patient-control status.

death group for the 4-3 and 4-4 phenotype groups. There were 16 Afro-American patients: 11 CAD deaths and 5 nonfatal myocardial infarctions. The overall results were similar whether or not the Afro-Americans were included. The apolipoprotein E gene frequencies for Afro-American patients were ε2 (0.06), ε3 (0.69) and ε4 (0.25). The 38 Afro-American control subjects had the following gene frequencies: ε2 (0.08), ε3 (0.72) and ε4 (0.20).

To further evaluate the results, gene frequencies in the Multiple Risk Factor Intervention Trial (CAD deaths, myocardial infarctions and controls) for white men only were compared with similar data reported for the Framingham Study population.[28] The frequency of ε4 was 0.14 among the Framingham men versus roughly 0.13 for both the Multiple Risk Factor Intervention Trial controls and patients with myocardial infarction, compared with 0.24 for the Multiple Risk Factor Intervention Trial CAD deaths. This comparison provides external validity that there may indeed be an increased risk associated with ε4.

Analysis of variance was used to determine whether there was any relation between apolipoprotein E phenotypes and changes in LDL cholesterol in the Multiple Risk Factor Intervention Trial. There were no significant differences in changes in LDL cholesterol over time by apolipoprotein E phenotype (Table IV). Those with nonfatal myocardial infarction had the largest change over the 6-year period, probably due to changes in diet or from the use of lipid-lowering drugs after myocardial infarction.

To determine whether the relation of risk factors with CAD varied by apolipoprotein E phenotype, further analyses were conducted. Differences in the levels of risk factors between cases of CAD and controls within apolipoprotein E phenotypes are presented in Table V. The 3 E 2-2s were combined with the E 3-2s and the 16 E 4-4s with the E 4-3s. The myocardial infarctions and CAD deaths were also combined as cases of CAD because of relatively small numbers. Consistent with the overall Multiple Risk Factor Intervention Trial study results, cigarette smoking was greater among patients than control subjects in all 3 groupings. Total cholesterol also tended to be higher among patients than among control subjects. There was no evidence of interaction with major risk factors and apolipoprotein E phenotype with the exception of plasma triglycerides ($p = 0.05$ for interaction). This interaction arises because, among E 3-3 participants, patients had higher triglyceride levels than control subjects (230 vs. 183 mg/dl, $p = 0.01$) whereas among E 4-3, 4-4 participants, patients had lower triglycerides than control subjects (186 vs 214 mg/dl, $p = 0.18$). Among E 2-2, 3-2 participants, triglycerides were similar for patients and control subjects (244 vs 237 mg/dl, $p = 0.87$).

DISCUSSION

Results from the present study demonstrate that E4 is a risk factor for CAD after accounting for baseline LDL cholesterol and other possible confounding variables, such as body mass index, HDL cholesterol, cigarette use and diastolic blood pressure. Because the results remained significant after adjustment for LDL cholesterol, the differences are not simply attributable to differences in lipid levels between phenotypes. The apolipoprotein E polymorphism may have an effect on CAD risk distinct from its effect on baseline lipoprotein levels for the following possible reasons: (1) Subjects with E4 may have had a higher LDL cholesterol for a longer period of time than E 3-3 subjects with similar LDL cholesterol at entry to the study. If the increase in LDL cholesterol with age occurred earlier with E4, then the extent of atherosclerosis, as a measure of level and duration, may have been greater. Recent studies from Finland and Italy noted higher LDL cholesterol among children who were carriers of E4 than E2 or E3.[29,30] This finding would be consistent with the results from the Pathobiological Determinants of Atherosclerosis in Youth research group. (2) There may be a difference in the metabolism of lipoproteins in relation to apolipoprotein E phenotype that affects atherosclerosis, or possibly thrombosis, independent of LDL cholesterol levels. (3) Differences in clearance of chylomicrons and remnant particles after a meal are different by apolipoprotein E phenotype and may be related to risk of disease.[31]

Patients and control subjects with the E 4-3 and 4-4 phenotypes had higher levels of LDL cholesterol than E 2-2 and 3-2 (Table V). Higher LDL cholesterol levels in E4 carriers means that patients with the same LDL cholesterol level but with different apolipoprotein E phenotypes will be in a different percentile distribution of the LDL cholesterol curve than others of the same phenotype. Therefore, using any general cutoff point for LDL cholesterol, such as 130 or 160 mg/dl, will result in a different percentage of subjects being selected as being hyperlipidemic based on their apolipoprotein E phenotype. We do not know whether a person who is an E 3-2 with an LDL cholesterol of 160 mg/dl may be at a different risk than one who is an E 4-3 or 3-3 with an LDL cholesterol of the same level. Clearly the E 3-2 person with a 160 mg/dl LDL cholesterol will be at the tail of the distribution of LDL cholesterol of all individuals with the E 3-2 phenotype, whereas the person with an E 4-3 or 3-3 phenotype with a similar cholesterol level will be more toward the average or mean LDL cholesterol for those with that phenotype. It is not known whether the absolute level of LDL cholesterol or the percentile distribution of LDL cholesterol for an individual is a more important determinant of risk of CAD.

Several previous studies have suggested that there may be an interaction between apolipoprotein E phenotype and response to various interventions for lowering LDL cholesterol.[32-34] The Multiple Risk Factor Intervention Trial did not demonstrate any substantial differences between apolipoprotein E groups in changes in LDL cholesterol over time. The overall changes in LDL cholesterol in the Multiple Risk Factor Intervention Trial were relatively small. The laboratory measurements were very carefully monitored to reduce the likelihood of laboratory drift over time. Furthermore, laboratory tests were performed in the same manner for participants with different apolipoprotein E phenotypes and special and usual care. Laboratory variability is unlikely to account for the absence of an intervention effect by apolipoprotein E phenotypes. These findings from the Multiple Risk Factor Intervention Trial certainly do not rule out the possibility that apolipoprotein E phenotypes may play a role in LDL response to either diet or specific drug therapy, or an interrelation between apolipoprotein E phenotype, postprandial response to diet, or variations in triglyceride metabolism. It might be particularly interesting to evaluate the effects of weight loss and variations in specific types of lipid-lowering diets on changes in triglycerides, HDL cholesterol, and LDL cholesterol in relation to apolipoprotein E phenotype.

The different association between triglyceride levels and risk of CAD according to E 3-3 phenotype has not been previously reported. This may be chance observation. It would be worthwhile to try and replicate these observations in other studies.

REFERENCES

1. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis* 1988;8:1–21.

2. Eichner JE, Kuller LH, Ferrell RE, Meilahn EN, Kamboh MI. Phenotypic effects of apolipoprotein structural variation on lipid profiles: III. Contribution of apolipoprotein E phenotype to prediction of total cholesterol, apolipoprotein B, and low density lipoprotein cholesterol in the Healthy Women Study. *Arteriosclerosis* 1990;10:379–385.

3. Scott J, Knott TJ, Shaw DJ, Brook JD. Localization of the genes encoding apolipoproteins CI, CII, and E to the p13 → cen region of human chromosome 19. *Hum Genet* 1985;71:144–146.

4. Rall SC, Weisgraber KH, Mahley RW. Human apolipoprotein E: the complete amino acid sequence. *J Biol Chem* 1982;257:4171–4178.

5. Weisgraber KH, Innerarity TL, Mahley RW. Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site. *J Biol Chem* 1982;257:2518–2521.

6. Mahley RW, Innerarity TL. Lipoprotein receptors and cholesterol homeostasis. *Biochim Biophys Acta* 1983;737:197–222.

7. Gregg RE, Zech LA, Schaefer EJ, Brewer HB. Type III hyperlipoproteinemia: defective metabolism of an abnormal apolipoprotein E. *Science* 1981;211:584–586.

8. Gregg RE, Zech LA, Schaefer EJ, Brewer HB. Apolipoprotein E metabolism in normolipoproteinemic human subjects. *J Lipid Res* 1984;25:1167–1176.

9. Gregg RE, Zech LA, Schaefer EJ, Stark D, Wilson D, Brewer HB. Abnormal in vivo metabolism of apolipoprotein E_4 in humans. *J Clin Invest* 1986;78:815–821.

10. Gregg RE, Brewer HB. The role of apolipoprotein E and lipoprotein receptors in modulating the in vivo metabolism of apolipoprotein B-containing lipoproteins in humans. *Clin Chem* 1988;34:B28–B32.

11. Demant T, Bedford D, Packard CJ, Shepherd J. Apolipoprotein B-100 metabolism in normolipidaemic subjects homozygous for different apolipoprotein E isoforms. In: Shephered J, Packard CJ, Brownlie SM, eds. Lipoproteins and the Pathogenesis of Atherosclerosis. Proceedings of the International Symposium on lipoproteins and the pathogenesis of atherosclerosis. Gleneagles, Perthshire, 24–27 February 1991. Amsterdam; Elsevier Science BV, 1991:3–12.

12. Cumming AM, Robertson FW. Polymorphism at the apoprotein-E locus in relation to risk of coronary disease. *Clin Genet* 1984;25:310–313.

13. Kuusi T, Nieminen MS, Ehnholm C, Yki-Järvinen H, Valle M, Nikkilä EA, Taskinen M-R. Apoprotein E polymorphism and coronary artery disease. Increased prevalence of apolipoprotein E-4 in angiographically verified coronary patients. *Arteriosclerosis* 1989;9:237–241.

14. Utermann G, Hardewig A, Zimmer F. Apolipoprotein E phenotypes in patients with myocardial infarction. *Hum Genet* 1984;65:237–241.

15. Menzel H-J, Kladetzky R-G, Assman G. Apolipoprotein E polymorphism and coronary artery disease. *Arteriosclerosis* 1983;3:310–315.

16. Eto M, Watanabe K, Makino J. Increased frequencies of apolipoprotein E2 and E4 alleles in patients with ischemic heart disease. *Clin Genet* 1989;36:183–188.

17. Nieminen MS, Mattila KJ, Aalto-Setälä K, Kuusi T, Kontula K, Kauppinen-Mäkelin R, Ehnholm C, Jauhiainen M, Valle M, Taskinen M-R. Lipoproteins and their genetic variation in subjects with and without angiographically verified coronary artery disease. *Arteriosclerosis and Thrombosis* 1992;12:58–69.

18. Gylling H, Aalto-Setälä K, Kontula K, Miettinen TA. Serum low density lipoprotein cholesterol level and cholesterol absorption efficiency are influenced by apolipoprotein B and E polymorphism and by the FH-Helsinki mutation of the low density lipoprotein receptor gene in familial hypercholesterolemia. *Arteriosclerosis and Thrombosis* 1991;11:1368–1375.

19. Hixson JE and the PDAY Research Group. Apolipoprotein E polymorphisms affect atherosclerosis in young males. *Arteriosclerosis and Thrombosis* 1991;11:1237–1244.

20. Multiple Risk Factor Intervention Trial Research Group: Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA* 1982;248:1465–1477.

21. Multiple Risk Factor Intervention Trial Research Group. Mortality rate after 10.5 years for participants in the Multiple Risk Factor Intervention Trial. Findings related to a priori hypothesis of the trial. *JAMA* 1990;263:1795–1801.

22. Cauley JA, Gutai JP, Kuller LH, Dai WS for the Multiple Risk Factor Intervention Trial Research Group. Usefulness of sex steroid hormone levels in predicting coronary artery disease in men. *Am J Cardiol* 1987;60:771–777.

23. Multiple Risk Factor Intervention Trial Research Group: coronary heart disease death, non-fatal acute myocardial infarction and other clinical outcomes in the Multiple Risk Factor Intervention Trial. *Am J Cardiol* 1986;58:1–13.

24. Widdowson GM, Kuehnemann M, DuChene AG, Hulley SB, Cooper GR. Quality control of biochemical data in the Multiple Risk Factor Intervention Trial: Central Laboratory. *Controlled Clin Trials* 1986;7:17S–33S.

25. Eichner JE, Kuller LH, Ferrell RE, Kamboh MI. A simplified method for screening the apolipoprotein E polymorphism. *Hum Hered* 1991;41:61–64.

26. Snedecor GW, Cochran WG. Statistical Methods. Iowa City, IA. Iowa State University Press, 1967.

27. Breslow N, Day N. Statistical Methods in Cancer Research, vol. I. The Analysis of Case-Control Samples. Lyon, France: International Agency for Research on Cancer (IARC) Scientific Publications, no. 32, 1980.

28. Ordovas JM, Litwack-Klein L, Wilson PWF, Schaefer MM, Schaefer EJ. Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE_1 and apoE_5 isoforms. *J Lipid Res* 1987;28:371–380.

29. Lehtimäki T, Moilanen T, Vükari J, Akerblom HK, Ehnholm C, Rönnemaa T, Marniemi J, Dahlen G, Nikkari T. Apolipoprotein E phenotypes in Finnish youths: a cross-sectional and 6-year follow-up study. *J Lipid Res* 1990;31:487–495.

30. Xu C-F, Talmud PJ, Angelico F, DelBen M, Savill J, Humphries SE. Apolipoprotein E polymorphism and plasma lipid, lipoprotein, and apolipoprotein levels in Italian children. *Genet Epidemiol* 1991;8:389–398.

31. Brown AJ, Roberts DCK. The effect of fasting triacylglyceride concentration and apolipoprotein E polymorphism on postprandial lipemia. *Arteriosclerosis and Thrombosis* 1991;11:1737–1744.

32. Tikkanen MJ, Huttunen JK, Ehnholm C, Rietinen P. Apolipoprotein E_4 homozygosity predisposes to serum cholesterol elevation during high fat diet. *Arteriosclerosis* 1990;10:285–288.

33. Weintraub MS, Eisenberg S, Breslow JL. Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. *J Clin Invest* 1987;90:1571–1577.

34. Nestruck AC, Bouthillier D, Sing CF, Davignon J. Apolipoprotein E polymorphism and plasma cholesterol response to probucol. *Metabolism* 1987;36:743–747.

Value of Rest Thallium-201/Technetium-99m Sestamibi Scans and Dobutamine Echocardiography for Detecting Myocardial Viability

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The relation between radioisotopic and echocardiographic markers of myocardial viability and postrevascularization recovery of function is still to be defined. To this purpose, 14 patients (11 men, 3 women, aged 35 to 64 years, mean 54 ± 7) with ventricular dysfunction were studied by a multiparametric approach. Each patient underwent, on separate days, rest thallium-201 and technetium-99m sestamibi scintigraphy, dobutamine echocardiography and coronary angiography. Coronary angiography was analyzed by a quantitative approach. Thallium uptake at rest was quantified from planar early (10-minute) and delayed (16-hour) thallium-201 images and expressed as a percentage of maximal activity in each projection using a 13-segment model. Sestamibi uptake was expressed in the same way. Dobutamine (up to 10 μg/kg/min) echocardiography was analyzed using a score index ranging from 1 (normokinesia) to 4 (dyskinesia) and a similar segmental model. Before revascularization 50 segments were grouped as normal (coronary stenosis <50% and normal function, group 1); of the remaining 132 segments with >50% coronary stenosis, 57 had normal wall motion (group 2) and 75 showed regional dyssynergies (group 3). Early and delayed thallium-201 regional percent activities did not differ in group 1 and in group 2 but were significantly less in group 3 segments. Sestamibi percent activity was more in group 1 and significantly reduced both in group 2 and 3 segments. Segments with improved wall motion after dobutamine had more early, delayed thallium-201 and sestamibi percent activities than unresponsive segments. Postrevascularization echocardiography was performed in all patients. Delayed thallium-201 scans and dobutamine echocardiography showed good sensitivity and specificity in detecting viable myocardium. It is concluded that: (1) rest-injected, delayed thallium-201 scan provides a good preoperative characterization of viable myocardium; (2) sestamibi does not differentiate dyssynergic from normal segments in territories supplied by stenotic coronary arteries; and (3) dobutamine echocardiography is similar to delayed thallium-201 scintigraphy in predicting myocardial viability.

(Am J Cardiol 1993;71:166–172)

The clinical concept that absence of thallium-201 redistribution after a stress study indicates the presence of necrotic myocardium has been challenged by recent descriptions of delayed imaging or reinjection techniques.[1,2] These new protocols have shown that apparent 4-hour "persistent defects" frequently overestimate myocardial scarring and that these defects may be reversed either by tracer reinjection or by delaying the control scan up to 72 hours. This "reinjection" or "late" reversibility was shown to be a reliable marker of myocardial viability when compared with perfusion/metabolic imaging using positron emission tomography[2] or recovery of function after coronary revascularization.[3] In these studies, in the case of severe coronary stenosis, thallium-201 delivery may be reduced due to the absence of poststress hyperemia, to the presence of severe hypoperfusion at rest, to the occurrence of long-lasting metabolic abnormalities, and to the lower plasma tracer concentration.[4,5] Accordingly, the induction of myocardial ischemia appears to be a limiting factor when the main question is sizing myocardial infarction or viable areas, or both. A more rational approach could be based on rest injected thallium imaging alone. Recently, the physical properties of technetium (Tc)-99m sestamibi (sestamibi) have expanded the diagnostic yield of this Tc-99m-based compound from the assessment of transient ischemia to the estimation of salvaged myocardium after thrombolytic therapy.[6,7] However, whether rest sestamibi uptake reflects viability beyond blood flow distribution is still to be defined. Published data suggest that sestamibi activity may be depressed in segments with normal wall motion and that regions with markedly reduced uptake at rest may contain viable myocardium.[8,9] Finally, echocardiography during dobutamine infusion has been shown to accurately unmask viable myocardium detected by positron emission tomography and confirmed by long-term func-

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From the CNR Institute of Clinical Physiology, Pisa, Italy. This study was supported in part by CNR-targeted project "Prevention and Control Disease Factors," subproject "Control of Cardiovascular Disease," from the National Research Council, Rome, Italy, and by Ministero Pubblica Istruzione, Rome, Italy. Manuscript received May 20, 1992; revised manuscript received and accepted August 12, 1992.

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TABLE I Individual Data in 14 Patients with Previous Myocardial Infarction

Case No.	Age (yr) & Sex	Site of MI	Interval AMI (wks)	Percent Diameter			LVEF (%)	Type Revasc.	F-U (wks)
				LAD	LC	Right			
1	53M	Anterior	36	74	87	Ø	46	CABG	10
2	59M	Inferior	49	75	100	100	30	CABG	8
3	53M	Inferior	14	55	69	100	50	CABG	15
4	57M	Anterior	98	100	91	Ø	41	CABG	14
5	64M	Inferior	32	Ø	100	80	47	CABG	13
6	55F	Anterior	21	79	100	70	30	CABG	8
7	61M	Anterior	19	87	Ø	91	36	CABG	12
8	51F	Inferior	26	100	90	72	35	CABG	15
9	49M	Anterior	18	Ø	86	100	38	CABG	11
10	55M	Anterior	70	100	92	85	32	PTCA	12
11	59M	Inferior	25	81	Ø	100	48	PTCA	13
12	63F	Anterior	9	100	20	79	41	PTCA	10
13	51M	Anterior	24	96	Ø	73	28	PTCA	11
14	35M	Interior	52	Ø	Ø	95	44	PTCA	11

CABG = coronary artery bypass surgery; F-U = follow-up interval; LAD = left anterior descending coronary artery; LC = left circumflex artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; Type Revasc. = type of coronary revascularization; Ø = coronary stenosis <50%.

tional recovery.[10,11] The head-to-head comparison between conventional radioisotopic methods and dobutamine echocardiography in characterizing reversible asynergic segments as well as the direct analysis of thallium-201 and sestamibi uptakes in the same study population have not been reported. The present study compares rest thallium-201 and sestamibi uptakes and dobutamine echocardiography in different categories of segments before coronary revascularization to assess their predictive accuracy in estimating postrevascularization functional recovery, the most accurate index of potential viability.

METHODS

Study group: The study group consisted of 14 patients (11 men and 3 women, aged 35 to 64 years [mean 54]) with regional wall motion abnormalities at rest due to previous myocardial infarction, who were referred to the nuclear cardiology laboratory for the assessment of myocardial viability. Patients with recent myocardial infarction or unstable angina were not studied. All patients were studied by sestamibi scintigraphy within 1 week of the thallium-201 scan. Previous myocardial infarction had occurred in all patients ≥6 weeks before the first scintigraphic study and was documented in all by elevated serum creatine kinase isoenzymes and electrocardiographic changes. The site of myocardial infarction was anterior in 8 patients and inferior in 6 (Table I). Medical therapy was discontinued ≥24 hours before all scans; no patient was receiving β blockers at the time of the radioisotopic, echocardiographic or ventriculographic study. All patients gave their informed consent as part of a protocol approved by the Ethical Committee on Human Studies of the Hospital of Pisa on December 10, 1990.

To compare the different categories of segments before and independently of the follow-up study all segments were grouped according to coronary anatomy and regional function into 3 subsets: group 1, normal function and absence of significant coronary stenosis; group 2, segments with normal function but significant coronary stenosis; and group 3, dyssynergic segments in vascular stenotic territories. As an additional inclusion criterion, all patients underwent a successful revascularization procedure, consisting of coronary bypass grafting in 9 patients and coronary angioplasty in the remaining 5 patients.

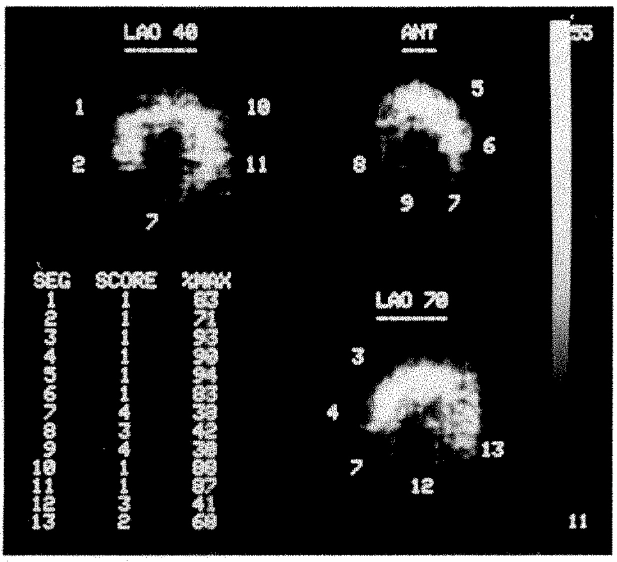
Sestamibi imaging protocol: Each patient was administered 15 mCi (555 MBq) of sestamibi (Du Pont de Nemours, Germany; dose range 10 to 22 mCi). Imaging commenced at 60 to 90 minutes after tracer injection in the anterior projection, followed sequentially by 45° and 70° left anterior oblique projections. All sestamibi images were recorded in preset count, typically with a collection of ≥1 million counts on a small field-of-view mobile camera (Apex 415M, Elscint, Israel). A high-resolution, parallel-hole collimator and a 20% window centered on the 140 keV gamma ray peak of Tc-99m were used.

Thallium-201 imaging protocol: Patients were injected at rest with a mean of 2 mCi (74 MBq) of thallium-201; at 10 minutes after injection, imaging commenced in the same sequence described for sestamibi to obtain the early distribution of the tracer. The same sequence was repeated 16 hours (range 14 to 17) after the initial injection. All images were recorded in preset count collecting an average of 300,000 counts on the same camera used for sestamibi images, but having a 20% window centered on the 80 keV x-ray peak of thallium-201.

The total body exposure per patient averaged 1.9 MGy (0.19 rad) for the entire protocol.

Scintigraphic analysis: Rest left ventricular sestamibi and thallium-201 uptakes were assessed both qualitatively and quantitatively. Qualitative assessment of tracer uptake was performed by 2 investigators who were unaware of the results of coronary angiography and echocardiography. All myocardial segments were scored on a 4-point scale, from 1 = normal uptake to 4 = severely reduced or absent activity. In case of disagreement, decision was reached by consensus. The distribution of sestamibi and thallium-201 was analyzed in each of the standard 13 segments generally used for planar perfusion studies. Each segment was then assigned to 1 of the 3 coronary vascular territories as previously described.[12] Assignment of the apex to a specific coronary territory was variable and based on the coronary angiogram as well as on the presence of adjacent defects. A total of 182 territories was identified and analyzed in the 14 patients with ventricular dysfunction. Quantitative assessment of sestamibi and thallium-201 images was performed in the same segments. Briefly, sestamibi images were quantitated by performing modified interpolative background adjusted to handle studies of planar Tc-99m agents.[13] Quantitation of thallium-201 studies was undertaken by first performing background subtraction as described by Goris et al.[14] Left ventricular wall activity was subdivided into the same 13 segments of equal length used for qualitative analysis. The count activities within the myocardial sectors were expressed as a percentage of the peak activity in each view. Examples of defects by qualitative and quantitative analysis are shown in Figure 1.

Dobutamine echocardiography: Commercially available wide-angle phased-array imaging systems (Hewlett-Packard 77020 or Toshiba Sonolayer FFA270A, 2.5 and 3.5 MHz transducers) were used. The left ventricle was divided into 13 segments: apex; proximal and distal septal, anterior, anterolateral, posterolateral, posterior and inferior wall. This segmentation was adapted following the 20-segment model proposed by the American Society of Echocardiography,[15] with the apex considered as a single segment and only 2 septal segments taken into account in order to match the nuclear segmentation. According to the recommendations of the American Society of Echocardiography, segmental wall motion was graded as: normal (score = 1), hypokinetic (score = 2), akinetic (score = 3), or dyskinetic (score = 4). The initial dobutamine infusion rate was 5 μg/kg/min followed by 10 μg/kg/min, with each dose lasting for 5 minutes, under electrocardiographic and echocardiographic monitoring. The recordings on videotape were analyzed off-line by 2 experienced independent observers unaware of the clinical, angiographic and scintigraphic data. All segments were scored basally and as a responder to dobutamine, or improved at the follow-up study when their segmental score decreased by a factor of 1 or more compared with the respective baseline value. Of the total 182 segments scored in all conditions, a unanimous decision was reached in 167 (92%), whereas in the remaining segments a split decision was resolved by consensus.



SEG	SCORE	%MAX
1	1	83
2	1	71
3	1	93
4	1	90
5	1	94
6	1	83
7	4	38
8	3	42
9	4	38
10	1	88
11	1	87
12	3	41
13	2	68

FIGURE 1. Analysis of the regional tracer activities was performed for thallium-201 and sestamibi by dividing 3 images (left anterior oblique [LAO] 40, anterior [ANT] and LAO 70) into 13 segments (SEG): proximal and distal septal, anterior, anterolateral, posterolateral, inferior, posterior and the apex. A normal activity is evident in all segments except 7, 8, 9, 12 and 13. The quantitative analysis (%MAX) displayed for each segment shows a close correlation with qualitative data (SCORE).

Coronary angiography and contrast ventriculography: All patients underwent coronary angiography in multiple projections, and left ventriculograms were obtained in biplane views within 2 weeks from radioisotopic and echocardiographic studies. All angiograms were reviewed by an independent expert who had no knowledge of the scintigraphic and echocardiographic results. Digital computer-assisted calipers (Kontron, Germany) were used to measure stenotic arterial segments that were quantified as minimal cross-sectional area. Stenoses of >50% reduction in the normal cross-sectional area were considered significant. Collateral circulation was graded visually on a binary scale depending on the degree of opacification of the occluded vessel: 0 = no opacification or filling of side branches without opacification of the epicardial vessel, and 1 = partial or complete filling of the occluded vessel via collateral vessels. Only vessels with a score of 1 were considered to be supplied by a well-developed collateral circulation.

Follow-up study: During revascularization procedures an attempt was made to revascularize all major branch vessels with ≥50% stenosis independently of the demonstration of regional myocardial viability. Baseline echocardiography was obtained in all patients at an average of 11 ± 2 weeks after coronary angioplasty or surgery; no patient had clinical evidence of perioperative or postangioplasty myocardial infarction or restenosis, nor was any patient receiving β blockers or inotropic drugs at the time of this echocardiographic evaluation. A segment was defined viable when regional wall motion improved by >1 echocardiographic grade after coronary recanalization.

Statistical analysis: Data are presented as mean ± SD. Sequential measurements were compared by repeated-measures analysis of variance and significant differences between any groups were sought by means of Newman-Keuls multiple range test. Differences in quantitative mean percent peak activity in different groups were analyzed by means of unpaired *t* test. Each group of values was compared with all the others. A p value <0.05 was considered significant. Confidence intervals for sensitivity and specificity for each technique were calculated according to the method described by Diamond.[16]

RESULTS

Baseline study: GENERAL FINDINGS IN THE STUDY POPULATION: Individual patient data are listed in Table I. All patients had coronary artery disease; coronary angi-

TABLE II Echocardiographic Score Index in the 75 Dyssynergic Segments in Group 3 at Baseline, During Dobutamine Infusion and at Follow-Up Study

	Dobutamine			Follow-Up		
Baseline	Normal	Hypokinetic	Akinetic	Normal	Hypokinetic	Akinetic
35 hypokinetic	26	9	0	30	5	0
40 akinetic	3	16	21	4	15	21

ography showed 1-, 2- and 3-vessel disease in 1, 8 and 5 patients, respectively. Average ejection fraction was 39 ± 7%. Exercise stress test was positive in 9 patients and negative in 5; average rate-pressure products were not statistically different between the 2 groups (22,266 ± 6,267 vs 23,480 ± 3,514, p = NS). With few exceptions, radioisotopic quantitative analysis correlated well with qualitative data. Only 3 segments, 2 with a qualitative score of 2 and 1 with a score of 3, showed a mismatch when compared with the corresponding quantitative value for early and delayed thallium-201 scans. For sestamibi, 5 segments, 3 with a qualitative score of 2 and 2 with a score of 3, showed a similar mismatch. To allow a more accurate comparison with echocardiography and follow-up data and because of a satisfactory validation of quantitative analysis for both tracers,[2,6] only data from quantitative analysis have been used.

Results in different segment groups: Fifty segments had normal wall motion and coronary stenosis <50% (group 1). The remaining 132 segments, perfused by stenotic coronary arteries, were subdivided into group 2 (57 segments with normal wall motion) and group 3 (75 segments with wall motion abnormalities). Group 1 — average minimal cross-sectional area of the stenosis in the corresponding coronary artery was 26 ± 19%. Early and delayed thallium-201 activities averaged 78 ± 8 and 77 ± 9% of the peak activity (p = NS). Sestamibi activity was significantly greater in these segments than with early and delayed thallium-201 activity in the same segments (81 ± 9% of the peak, p <0.05). These values are similar to those previously reported both for thallium-201[17] and sestamibi studies[13] in segments without significant coronary arterial narrowing. Group 2 — the average minimal cross-sectional area of the stenosis was 85 ± 14%. In this group, early and delayed thallium-201 activities were 75 ± 9 and 74 ± 10% of the peak activity, respectively (p = NS). Sestamibi activity averaged 63 ± 8% of the peak (p <0.05 vs group 1 sestamibi activity) and was significantly less than early and delayed thallium-201 activities in these segments (p <0.05). Group 3 — this group consisted of 75 segments with wall motion abnormalities and an average cross-sectional area of 93 ± 9%. This value was significantly greater than that observed in group 2 segments (p <0.05). Early and delayed thallium-201 activities averaged 62 ± 14 and 59 ± 13% of the peak activity (p <0.05 vs group 1 and 2 early and delayed thallium-201 activities, respectively). Sestamibi activity averaged 60 ± 15% of the peak; this value was statistically less than the group 1 value (p <0.05) but was not different from the average sestamibi activity detected in segments of group 2. Percent radioisotopic activities in the 3 groups are shown in Figure 2.

Dobutamine echocardiography: No segment was scored as dyskinetic in any condition; echocardiographic signs of ischemia at the infusion rate of 10 μg/kg/min were never observed in groups 2 and 3. During the entire study, population rate-pressure products did not increase by >20% on the average. Of the 75 segments of group 3, 45 showed an improvement in regional wall motion after administration of dobutamine and 30 remained unchanged (Table II). Average coronary stenoses were not significantly different between segments with and without an improvement in regional wall motion after dobutamine infusion (91 ± 8 vs 95 ± 7%, p = NS). Early and delayed thallium-201 and sestamibi activities in dobutamine-responder segments were greater than those observed in nonresponder segments (68 ± 15, 69 ± 8 and 67 ± 13% vs 55 ± 11, 48 ± 8 and 52 ± 13% of the peak for early and delayed thallium-201 and sestamibi in the 2 subgroups, respectively; p <0.05 for all values).

Follow-up study: Five patients in our series underwent selective percutaneous transluminal coronary angioplasty and 9 patients coronary bypass surgery (Table I). In the surgically treated group, 21 stenotic vessels received a graft. In patients undergoing coronary angioplasty, 7 of 10 vessels were successfully dilated. The remaining 3 vessels were not related to segments in group

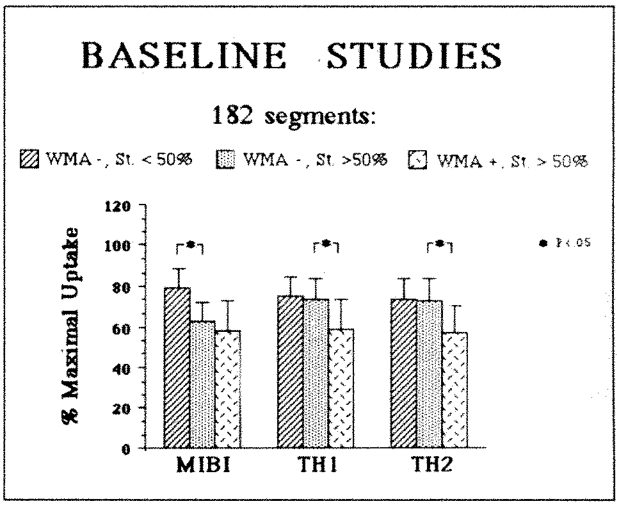


FIGURE 2. Quantitative analysis of rest sestamibi (MIBI), and 10-minute (TH1) and 16-hour (TH2) rest thallium uptake in the 182 segments relative to 14 patients. Sestamibi shows similar percent uptake to thallium-201 only in segments in group 1, without wall motion abnormalities (WMA) and coronary stenosis (St.), whereas it shows a definite intermediate reduction of uptake in segments in groups 2 and 3. When compared with the "on/off" signal of thallium-201, sestamibi shows a greater sensitivity to coronary stenosis independently of wall motion abnormalities. Only significant differences are shown.

TABLE III Sensitivity, Specificity and Relative Confidence Intervals of Each Technique

	Sensitivity (%)	CI (%)	Specificity (%)	CI (%)
Early thallium-201	79	61 to 94	73	45 to 82
Delayed thallium-201	86	85 to 99	92	59 to 90
Sestamibi	75	77 to 97	84	46 to 80
Dobutamine echocardiography	82	68 to 91	92	54 to 87

CI = confidence interval.

3. Of the 75 dyssynergic segments of group 3, 49, or 65%, showed an improved wall motion at follow-up study. In particular, 30 of the 35 basally hypokinetic segments showed normal wall motion at the follow-up examination. Of the 40 akinetic segments before coronary recanalization, 4 were classified as normal and 15 as hypokinetic at follow-up echocardiography (Table II). Average minimal lesion cross-sectional area was 91 ± 10 and 95 ± 4% in viable and nonviable segments, respectively (p = NS). Twenty-six of the 49 segments with improved wall motion showed a complete coronary occlusion, with grade 1 collateral circulation in 24. Of the 26 segments that did not benefit from coronary revascularization, 19 were related to a complete coronary occlusion with grade 0 collateral circulation in all. Rest early thallium-201, delayed thallium-201, sestamibi and dobutamine echocardiography correctly identified 79, 86, 75 and 82% and 73, 92, 84 and 92% of postoperative viable and nonviable segments, respectively. Sensitivity, specificity and the relative confidence intervals are summarized in Table III. The average percent activity of early and delayed thallium-201 and sestamibi in viable and necrotic segments, defined according to postoperative improvement in wall motion, was 67 ± 12, 67 ± 9 and 67 ± 13% vs 53 ± 12, 46 ± 6 and 48 ± 10% of the peak, respectively ($p < 0.05$ for all values). The number of segments that correlated with the presence of electrocardiographic Q waves was not different in viable (54%) versus nonviable (60%) segments. An example of multiple defects detected by thallium-201 and sestamibi in the same segments is shown in Figure 3.

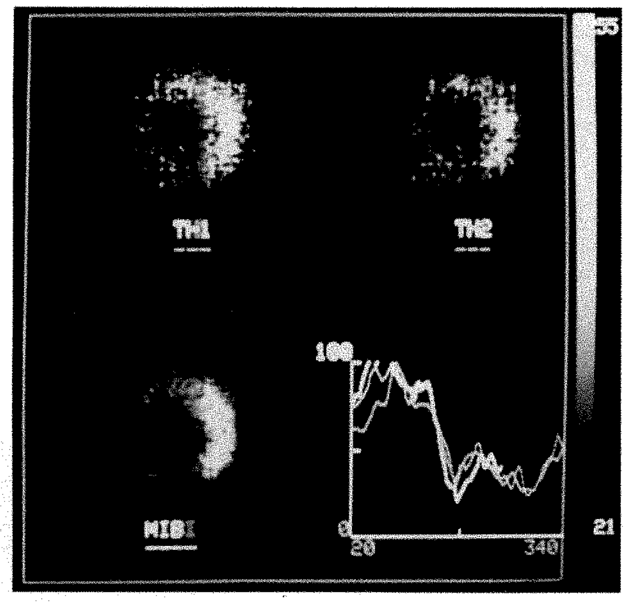


FIGURE 3. Background-subtracted left anterior oblique 40° projections obtained 10 minutes (TH1), 16 hours (TH2) and 90 minutes after rest thallium-201 and sestamibi (MIBI) injections in the same patient on separate days. Thallium-201 at 10 and 90 minutes and sestamibi show a severe uptake reduction at the upper and lower septum and at the apex. All distribution profiles *(lower right panel)* show the same reduction of tracer uptake in the same regions. These abnormal segments, all with a percent activity below lower normal limits for each tracer, did not show any improvement after revascularization.

DISCUSSION

In this study, we investigated the significance of rest thallium and sestamibi scintigraphy abnormalities, the response to dobutamine echocardiography and the degree of coronary stenosis in patients with abnormal regional wall motion undergoing coronary revascularization. Our data suggest that rest delayed thallium-201 can reliably separate viable from necrotic segments as accurately as dobutamine echocardiography. On the contrary, early thallium-201 and sestamibi showed the highest rate of false-positive and false-negative results.

Rest-injected thallium-201 imaging for the assessment of myocardial viability: According to the evidence provided by the reinjection protocol[2] and to the kinetics of potassium analogs, a rational basis for assessing myocardial viability could be limited to the rest images alone. Our results indicate that delayed thallium-201 has a good sensitivity and specificity in the preoperative identification of myocardial viability. Early thallium-201 images corresponding to the initial distribution of the tracer — which is mainly flow-dependent[18] — were less accurate and showed the highest rate of false-positives (false viability) in the follow-up study. The 7 false-positive segments by early thallium-201 showed an average percent activity of 67 ± 4 of the peak, whereas all showed a delayed thallium-201 value below 2.5 SD of normal segments. This finding can partly be explained by the presence of segments with an initial thallium-201 uptake that "leaks" out of necrotic cells, leaving a late quantitative defect correctly interpreted as necrosis. These kinetics have been partly demonstrated for rubidium-82,[19] but in principle could equally apply to thallium-201.[20] None of the patients with rest-rest reverse redistribution had had a non-Q-wave myocardial infarction, a condition that has been proposed as the mechanism underlying the "paradoxical" stress-rest thallium-201 defect.[21] Even though an early thallium-201 scan offers more imaging advantages, it does not provide the same values of sensitivity and specificity provided by the delayed scan. In this study we did not perform stress thallium-201 studies, and residual ischemia in these patients was ruled out by dipyridamole stress echocardiography.

Sestamibi as a potential marker of viability: Although the clinical efficacy of sestamibi as a perfusion tracer is similar to that of thallium-201,[22] its role in the clinical evaluation of myocardial viability is still unclear.[23,24] In this field, results from clinical studies are generally difficult to interpret because of the inability to distinguish between the contribution of flow and that of regional viability. Although published reports to date have demonstrated excellent agreement between the type of perfusion defects observed by sestamibi and by standard stress/redistribution thallium-201 scans, it remains to be seen whether recent thallium-201 protocols are superior to sestamibi images in assessing viability.[25]

The present data demonstrate that resting myocardial perfusion can be moderately reduced while contractile function is maintained. This is demonstrated in our series by the significant reduction in sestamibi versus both early and delayed rest thallium-201 activities in group 2 segments with normal wall motion and significant coronary artery stenosis. Whether this phenomenon actually reflects a greater sensitivity of sestamibi to moderate reduction in coronary blood flow at rest (Figure 4) needs to be defined in experimental models of graded, progressive coronary occlusion.

In the follow-up study, sestamibi showed the highest rate of false-negative (false-necrotic) results. Segments with low sestamibi uptake and recovery of function had an average sestamibi uptake of 46 ± 7% versus a delayed thallium-201 uptake of 60 ± 8% of the peak, respectively ($p < 0.05$). Again, sestamibi tended to underestimate viable myocardium in segments showing definite improvement in contractile function after coronary revascularization. These data would suggest that sestamibi is primarily a perfusion agent, less reliable than thallium-201 in estimating viability.

Dobutamine echocardiography: In this study echocardiography was used in conjunction with dobutamine to detect areas with residual viability. This was confirmed by the much greater early and delayed rest thallium-201 and sestamibi activities detected preoperatively in segments with a positive inotropic response to dobutamine as well as by a sensitivity and specificity in the follow-up study similar to those of delayed thallium-201 scan. These data are in agreement with experimental studies demonstrating a reversal of postischemic ventricular dysfunction after catecholamine infusion and with clinical studies in patients undergoing thrombolysis in the setting of acute myocardial infarction.[10,26] Our data extend previous observations on stunned myocardium[27] to a model, previous myocardial infarction with functional recovery after revascularization, in which the viable myocardium is more likely to be hibernated rather than stunned. This information can be obtained by means of a cheap, accurate, non–time-consuming and widely available technique. Recent acquisitions on the inotropic phase of dipyridamole testing[28] expand the role of echocardiography in defining myocardial viability.

Imaging strategy for detecting viable myocardium: Our results, demonstrating that rest-injected, delayed thallium-201 activity is a good predictor of postoperative improvement in regional wall motion, appear to be in agreement with the fundamental principles of thallium-201 kinetics. Rest protocols are simple and their application is rapidly diffusing in the nuclear medicine centers. Our data suggest that, similarly to stress scans,[2,29] rest studies also may take longer than 10 to 15 minutes for thallium-201 to reach the equilibrium in the potassium pool of the viable tissue, and that rest-injected thallium-201 delayed imaging can be considered a simple and relatively inexpensive technique to unmask viable myocardium.

When considering the results obtained with sestamibi, the main problem is that this tracer can be a marker of both rest hypoperfusion and viability. The improved myocardial thickening in the dyssynergic area induced by dobutamine as a marker of viability confirms the usefulness of this test to unmask viable myocardium in patients with wall motion abnormalities at rest.

Finally, quantitative coronary angiography did not prove to be useful in the search of viable myocardium because the same average coronary stenosis was found in viable and necrotic segments. However, in agreement with previous reports,[30] an efficient collateral circulation was present in 92% of viable and in none of necrotic segments, respectively.

Study limitations: Several limitations of the present study deserve further consideration. In this study we applied a rigid classification of segments based on presence or absence of coronary stenosis and wall motion abnormalities. It can be difficult sometimes to assign this or that segment to a definite category, and the limits of quantitative coronary angiography should also be considered. Dobutamine infusion was discontinued at 10 μg/kg/min and no information is available in these patients about the occurrence of myocardial ischemia with infusion rates of 20 and 40 μg/kg/min. Although only the 2 "low" doses were infused, this appeared to be sufficient to unmask viable myocardium in most of our patients. Even if commonly accepted segmentation

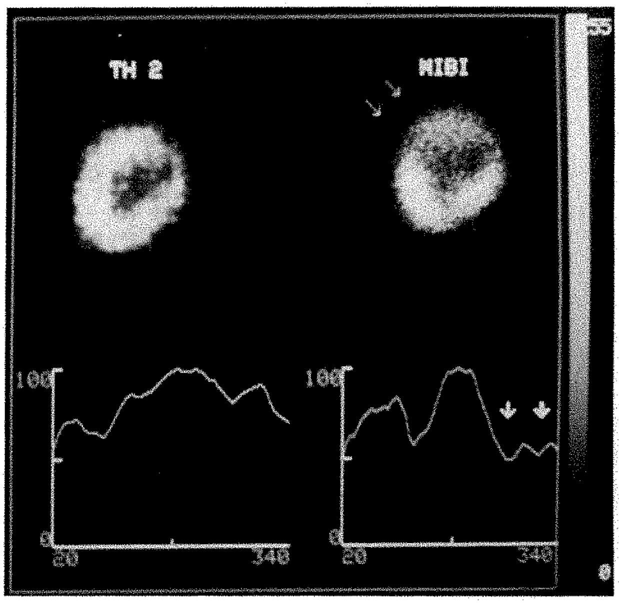


FIGURE 4. Background-subtracted left anterior oblique 70° projections obtained 16 hours after rest thallium-201 (TH 2) *(left panel)* and sestamibi (MIBI, *right panel*) injections in the same patient on different days. Thallium-201 image appears homogeneous, and activity profile normalized to maximal uptake *(lower left panel)* did not show any reduction below normal limits. Rest sestamibi image shows a defect in the proximal anterior segment that was confirmed by the severe reduction in sestamibi observed in the corresponding angular profile *(arrows)*. This patient had a 96% stenosis of the left anterior descending coronary artery with normal wall motion in this territory.

schemes for isotopic and echocardiographic data were used, the actual anatomic correlation is less than perfect. Although available in our institute, we did not use single-photon emission computed tomography protocols for 2 main reasons: (1) better standardization of quantitative analysis by planar techniques,[13] and (2) difficulty in obtaining thallium-201 delayed images with single-photon emission computed tomographic technology.[1,2]

To minimize the possible interaction between perfusion and function, we studied only patients with chronic coronary artery disease and excluded all patients with acute myocardial infarction. In these patients, sestamibi may detect — even with a single post-treatment baseline injection — low-risk patients in whom a small area at risk (ischemia + necrosis) warrants a more watchful approach.[7] Further clinical studies are needed to define the exact field of application of the 2 currently available tracers in this study population.

Clinical implications: The results of the present study suggest that delayed thallium-201 scan and dobutamine echocardiography can improve the differentiation of viable from nonviable myocardium. Whether these "cheap" signals provide comparable information to that of more sophisticated and expensive techniques, such as positron emission tomography, remains to be investigated. A cautious interpretation of fixed defects is required for early thallium-201 and sestamibi images to determine the extent of infarcted myocardium. Although both methods have sufficient sensitivity in identifying viable segments, their limits, i.e., under- and overestimation of myocardial viability, should also be considered.

Acknowledgment: We thank Claudio Marcassa, MD, and Monica Bartoli, RT, for help in collecting clinical studies, and Nadia Sereni and Ilaria Citti for technical assistance. We are also grateful to Dr. Antonio Caselli for his masterful editing of the manuscript, and to the Italian Byk Gulden for providing thallium-201.

REFERENCES

1. Kiat H, Berman DS, Maddahi J, De Yang L, Van Trian K, Rozansky A, Friedman A, Friedman S. Late reversibility of tomographic myocardial thallium- 201 defects: an accurate marker of myocardial viability. *J Am Coll Cardiol* 1988;12: 1456–1463.

2. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. Comparison of thallium scintigraphy with reinjection and PET imaging with 18-fluorodeoxyglucose. *Circulation* 1991;83:26–37.

3. Gibson RS, Watson DD, Taylor GJ, Crosby IK, Wellons HL, Holt ND, Beller GA. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. *J Am Coll Cardiol* 1983;1:804–815.

4. Budinger TF, Pohost GM, Bischoff P. Thallium-201 integral blood concentration over 2 hours explains persistent defects in patients with no evidence of MI by ECG (abstr). *Circulation* 1987;76(suppl IV):IV-64.

5. Camici P, Araujo LI, Spinks T, Lammertsma AA, Kaski JC, Shea MJ, Selwin AP, Jones T, Maseri A. Increased uptake of 18F-fluorodeoxyglucose in post- ischemic myocardium in patients with exercise induced angina. *Circulation* 1986;74:81–86.

6. Iskandrian AS, Heo J, Kong B, Lyons E, Marsh S. Use of technetium-99m isonitrile (RP-30A) in assessing left ventricular perfusion and function at rest during exercise in coronary artery disease and comparison with coronary arteriography and exercise thallium-201 SPECT imaging. *Am J Cardiol* 1989;64:270–275.

7. Wackers FJ, Gibbons RJ, Verani MS, Kayden DS, Pellika PA, Behereneck T. Serial quantitative planar technetium-99m isonitrile imaging in acute myocardial infarction: efficacy for noninvasive assessment of thrombolytic therapy. *J Am Coll Cardiol* 1989;14:861–873.

8. Parodi O, Marcassa C, Casucci R, Sambuceti G, Galli M, Inglese E, Marzullo P, Pirelli S, Bisi G, Giubbini R, Scopinaro R. Accuracy and safety of technetium-99m-hexakis 2-methoxy-2-isobutyl isonitrile (sestamibi) myocardial scintigraphy with high dose dipyridamole test in patients with effort angina pectoris: a multicenter study. *J Am Coll Cardiol* 1991;18:1439–1444.

9. Rocco TP, Dilsizian V, Strauss HW, Boucher CA. Technetium-99m isonitrile myocardial uptake at rest. II. Relation to clinical markers of potential viability. *J Am Coll Cardiol* 1989;14:1678–1684.

10. Pierard LA, de Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 1990;15:1021–1031.

11. Smart SC, Sawada SG, Ryan T, Atherton L, Segar DS, Bourdillon PDV, Armstrong WF, Feigenbaum H. Dobutamine echocardiography predicts recovery after thrombolysis in myocardial infarction (abstr). *Circulation* 1990;82:75.

12. Dilsizian V, Rocco TP, Strauss HW, Boucher CA. Technetium-99m isonitrile myocardial uptake at rest. I. Relation to the severity of coronary artery stenosis. *J Am Coll Cardiol* 1989;14:1673–1677.

13. Sinusas AJ, Beller GA, Smith WH, Winson EL, Brookeman W, Watson DD. Quantitative planar imaging with technetium-99m methoxy isonitrile: comparison of uptake patterns with thallium-201. *J Nucl Med* 1989;30:1456–1463.

14. Goris ML, Daspit SG, McLaughin P. Interpolative background subtraction. *J Nucl Med* 1976;17:44–47.

15. Schiller NB, Shah PM, Crawford M, De Maria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman AH, Tajik AJ. American Society of Echocardiography Committee on standards subcommittee on quantitation of two-dimensional echocardiograms: Recommendations for quantitation of the left ventricle by two dimensional echocardiography. *J Am Soc Echo* 1989; 2:358–367.

16. Diamond GA. Limited assurances. *Am J Cardiol* 1989;63:99–100.

17. Kaul S, Boucher CA, Newell JB, Chesler DA, Greenberg JM, Okada RD, Strauss HW, Dinsmore RE, Pohost GA. Determination of the quantitative thallium imaging variables that optimize detection of coronary artery disease. *J Am Coll Cardiol* 1986;7:527–537.

18. Melin JA, Becker L. Quantitative relationship between global left ventricular thallium uptake and blood flow: effects of propranol, ouabain, dipyridamole and coronary artery occlusion. *J Nucl Med* 1986;27:641–652.

19. Goldstein RA. Kinetics of rubidium-82 after coronary occlusion and reperfusion. *J Clin Invest* 1985;75:1131–1137.

20. Gould KI. Myocardial viability. *Circulation* 1991;83:333–335.

21. Weiss AT, Maddahi J, Lew AS, Shah PK, Ganz W, Swan HJC. Reverse redistribution of thallium-201: a sign of nontrasmural myocardial infarction with patency of the infarct related coronary artery. *J Am Coll Cardiol* 1986;7:61–67.

22. Kiat H, Maddahi J, Roy LT, Van Train K, Friedman J, Resser K, Berman DS. Comparison of Tc-99m methoxy isobutyl isonitrile with thallium-201 evaluation of coronary artery disease by planar and tomographic methods. *Am Heart J* 1989; 117:1–11.

23. Meerdink DJ, Thurber M, Savage S, Leppo JA. Effect of reperfusion and pacing on the myocardial extraction of thallium-201 and technetium-labelled analogue (RP30) (abstr). *J Am Coll Cardiol* 1988;11:33A.

24. Beanlands RSB, Dawood F, Wen W, McLaughlin PR, Butany Y, D'Amati G, Liu PT. Are the kinetics of technetium-99m methoxyisobutyl isonitrile affected by cell metabolism and viability? *Circulation* 1990;82:1802–1814.

25. Machac J. Technetium-99m isonitrile: a perfusion or viability agent. *J Am Coll Cardiol* 1989;14:1685–1688.

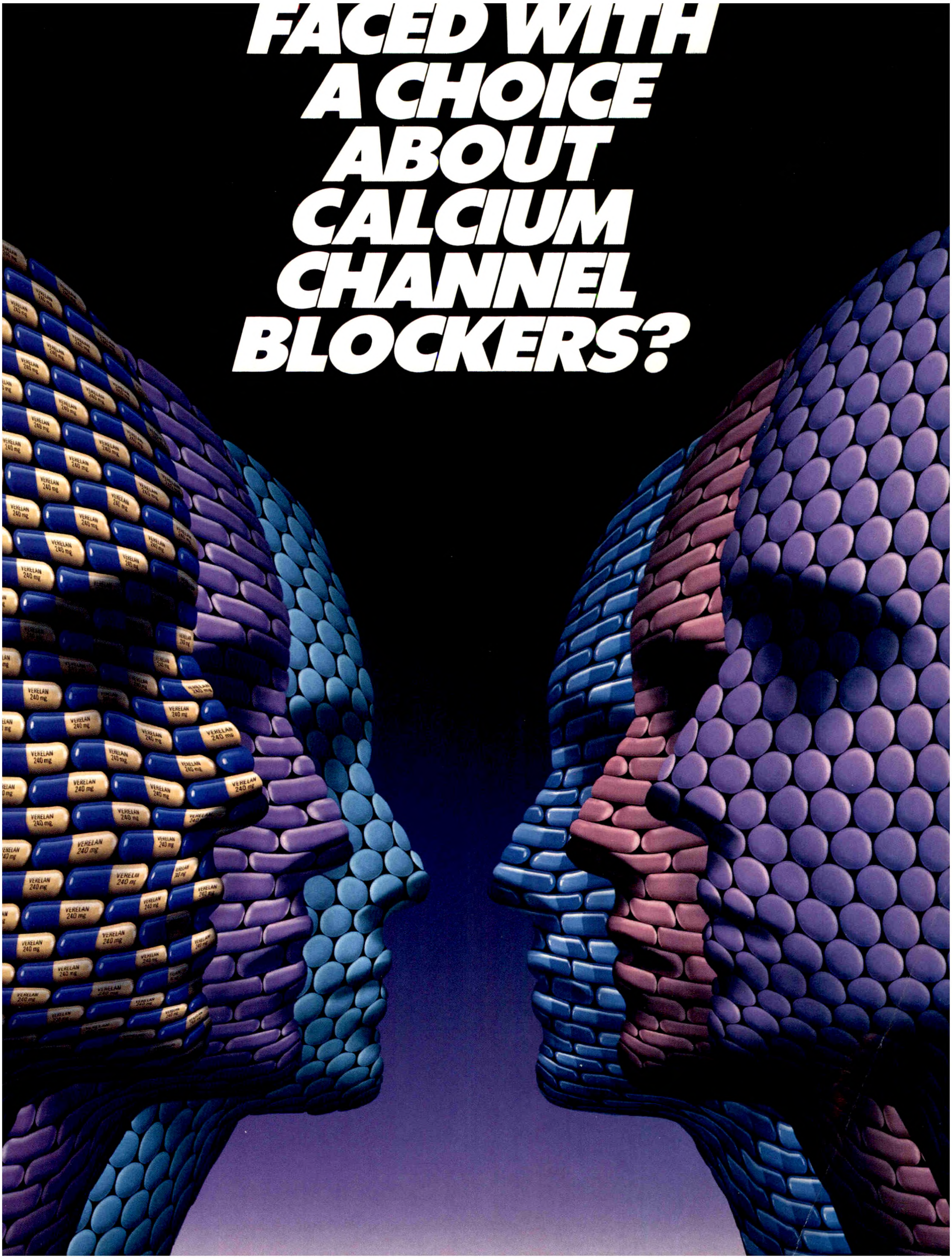
26. Ellis SG, Wynne J, Braunwald E, Henschke CI, Sandor T, Kloner RA. Response of reperfusion-salvaged, stunned myocardium to inotropic stimulation. *Am Heart J* 1984;107:13–19.

27. Bolli R, Zhu W, Myers ML, Hartley CJ, Roberts R. Beta-adrenergic stimulation reverse postischemic myocardial dysfunction without producing subsequent functional deterioration. *Am J Cardiol* 1985;56:964–968.

28. Picano E, Marzullo P, Gigli G, Reisenhofer B, Parodi O, Distante A, L'Abbate A. Identification of viable myocardium by dipyridamole-induced improvement in regional left ventricular function assessed by echocardiography in myocardial infarction and comparison with thallium scintigraphy at rest. *Am J Cardiol* 1992; in press.

29. Gutman J, Berman DS, Freeman M, Rozanski A, Maddahi J, Waxman M, Swan HJC. Time to completed redistribution of thallium-201 in exercise myocardial scintigraphy: relationship to the degree of coronary artery stenosis. *Am Heart J* 1983;106:989–995.

30. Fujita M, Ohno A, Wada O, Miwa K, Nozawa T, Yamanishi K, Sasayama S. Collateral circulation as a marker of the presence of viable myocardium in patients with recent myocardial infarction. *Am Heart J* 1991;122:409–414.



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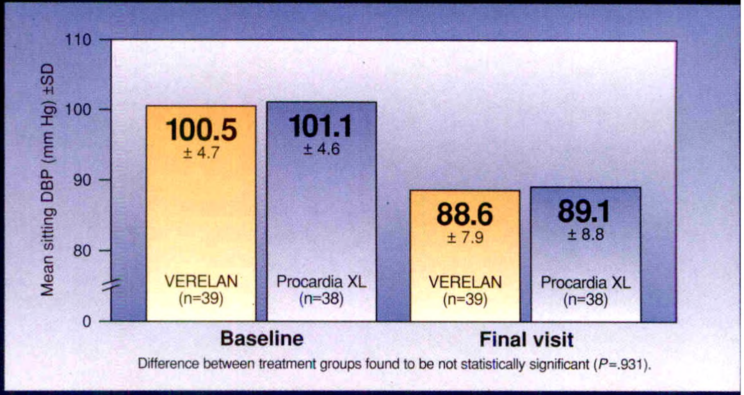

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Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on last page.

VERELAN

EXCELLENT TOLERABILITY SIMILAR TO PLACEBO IN A DOUBLE-BLIND STUDY[3,4]

ncidence of side effects commonly associated with calcium channel blockers

Side effect	VERELAN clinical trials[5] (n=285)	Double-blind, placebo-controlled study† VERELAN (n=81)	Placebo (n=26)
Constipation	7.4%	9.9%	11.5%
Headache	5.3%	7.4%	11.5%
Dizziness	4.2%	2.5%	3.8%
Edema	1.4%	3.7%	3.8%

esults of a 4-week, double-blind, placebo-controlled study of patients with sential hypertension. VERELAN 120 mg/day, n = 28; 240 mg/day, n = 27; 0 mg/day, n = 26; placebo, n = 26.

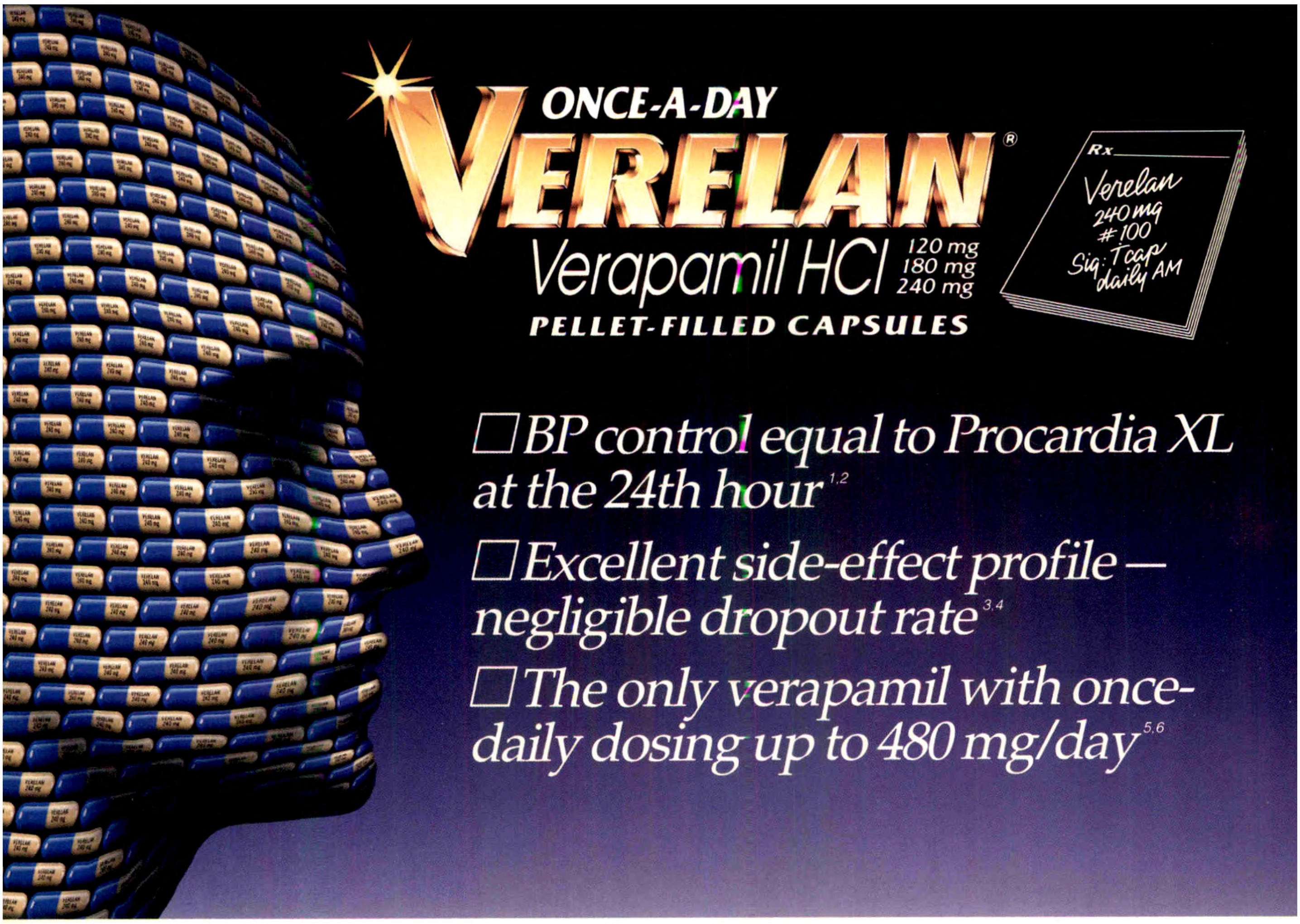
☐ No patients discontinued VERELAN therapy due to constipation, headache, dizziness, or edema

ONCE-A-DAY

VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES


ONCE-A-DAY
VERELAN®
Verapamil HCl
120 mg
180 mg
240 mg
PELLET-FILLED CAPSULES
Rx
Verelan
240 mg
#100
Sig: Tcap daily AM
☐ BP control equal to Procardia XL at the 24th hour[1,2]
☐ Excellent side-effect profile — negligible dropout rate[3,4]
☐ The only verapamil with once-daily dosing up to 480 mg/day[5,6]

References: 1. Levy B, Rosenberg LN, Colasante DA. A comparison of VERELAN® and Procardia® XL in the treatment of patients with mild to moderate hypertension. American College of Clinical Pharmacology. 21st Annual Meeting, 1992. Abstract. **2.** Further analysis of Levy B, et al. (See reference 1.) Data on file. Lederle Laboratories, Pearl River, NY. **3.** Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol*. 1991;31:144-150,490. **4.** Further analysis of Carr AA, et al. (See reference 3.) Data on file. Lederle Laboratories, Pearl River, NY. **5.** VERELAN Prescribing Information. **6.** *Physicians' Desk Reference®*, 46th ed. Montvale, NJ: Medical Economics Data; 1992:1181-1183 (Isoptin® SR) 2157-2159 (Calan® SR).

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment
increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicit
patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin.
digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually
an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given w
48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may
additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine
apy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Ve
amil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interacti
Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunte
clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a loweri
serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verap
bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclospo
Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardio
cular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizi
dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in
did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Catego**
There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregna
labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be disconti
during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been establis

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in a
ciation with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse react
were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%);
(1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of ve
amil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizzi
(3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary ed
(1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flus
(0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, mark
experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventricular dissocia
chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarr
dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Ner**
System: cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psyc
symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyper
tosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vi
Urogenital: gynecomastia, impotence, increased urination, spotty menstruation.

Rev.
2080

Lederle

Manufactured for
LEDERLE LABORATORIES DIVISION
American Cyanamid Company
Pearl River, NY 10965

by ELAN PHARMACEUTICAL RESEARCH CORP.
Gainesville, GA 30501

Advantus™ Pharmaceuticals

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September 1992

Printed in USA

Unrecognized Left Main Coronary Artery Disease in Patients Undergoing Interventional Procedures

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Katherine B. Kisslo, RDMS, Harry R. Phillips, MD, Thomas M. Bashore, MD,
Richard S. Stack, MD, and Charles J. Davidson, MD

Selective, coronary arteriographic, catheter-based, intravascular ultrasound images were obtained to determine the presence and extent of angiographically undetected or underestimated left main (LM) coronary arterial narrowing in patients receiving coronary interventional therapy. Coronary arteriograms were determined to be either normal or abnormal by visual inspection. Abnormal arteriograms were digitized and quantitated using a semiautomated edge-detection algorithm. Thirty-eight patients receiving percutaneous treatment of stenoses in the left coronary artery system were studied. Optimal LM coronary angiograms were obtained in 2 views, and intravascular ultrasound images were obtained after the coronary interventional procedure. Intravascular ultrasound detected plaque in 24 of 27 angiographically normal LM arteries (89%), whereas narrowing was observed in 11 of 11 angiographically abnormal LM arteries (100%). Eight of 38 patients (21%) had >40% area stenosis by intravascular ultrasound. In patients with angiographic disease, there was no correlation between quantitative angiographic and ultrasound percent area stenosis (r = 0.12; p = 0.72; SEE 19%). The median plaque area was not different between angiographically normal (0.05 cm^2; 0.03, 0.08 [25th, 75th percentile]) and abnormal (0.06 cm^2; 0.03, 0.1) patients. The median percent area stenosis in arteriographically normal subjects (26%; 14, 32%) was less than that in abnormal ones (37%; 20, 46%) (p = 0.03). Unrecognized LM disease is widespread and often underestimated in patients with normal LM angiograms undergoing interventional procedures. Plaque area is similar for angiographically normal and insignificantly abnormal vessels. This study suggests that intravascular ultrasound overcomes the limitations of silhouette imaging and can be a clinically useful, adjunctive method to evaluate LM coronary artery disease.

(Am J Cardiol 1993;71:173–176)

The presence of left main (LM) coronary artery disease can have important prognostic and therapeutic implications.[1] Given the high-profile, frequently rigid interventional devices that are now approved or undergoing development, even insignificant nonobstructive LM lesions (<50% angiographic diameter stenosis) may alter the percutaneous approach to a stenosis in the left coronary artery system. Despite its importance, LM disease is often neither accurately nor precisely evaluated by coronary angiography.[2,3] In an attempt to improve on angiographic techniques, catheter-based, intravascular ultrasound has been developed.[4–7] Unlike angiography, which produces longitudinal silhouette images of the coronary arteries, intravascular ultrasound generates tomographic images, enabling the detection of size, composition and topography of normal and atherosclerotic vascular structures. Recent studies demonstrated that intravascular ultrasound correlates well with histology and provides additional morphologic information in the setting of coronary interventions.[8–10] The purposes of this study were to determine, using intracoronary ultrasound, the presence, extent and composition of LM coronary artery disease in patients receiving interventional therapy in whom no angiographic LM abnormality was recognized before treatment, and to compare intravascular ultrasound and quantitative angiography in those with angiographically insignificant LM narrowings.

METHODS

Patients: Thirty-eight patients were studied (26 men and 12 women; mean age 57 ± 9 years). All patients were undergoing 1-vessel, coronary interventional procedures (balloon angioplasty alone [n = 28]; directional coronary atherectomy [n = 8]; and balloon angioplasty plus stent [n = 2]). Interventions were performed in the left anterior descending artery in 31 patients and the left circumflex artery in 7. Informed consent for coronary artery imaging in conjunction with coronary angioplasty or atherectomy was obtained from all patients.

Procedures: Before the intervention, diagnostic angiographic images were obtained of the LM coronary artery and target lesion. At least 2 orthogonal, unfore-

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From Duke University Medical Center, Durham, North Carolina. This study was supported in part by Grant 5T32 HL07101 from the National Institutes of Health, National Research Service Award, Bethesda, Maryland. Manuscript received April 21, 1992; revised manuscript received and accepted August 14, 1992.

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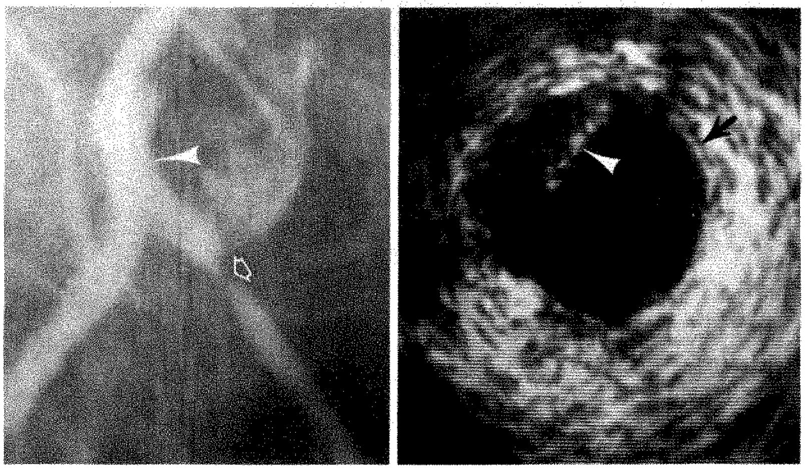

FIGURE 1. *Left,* representative right anterior oblique coronary arteriogram from angiographically normal patient with proximal left anterior descending stenosis *(open arrow).* Left main was normal *(solid arrow).* Corresponding intravascular ultrasound *(right)* demonstrates significant soft, eccentric plaque. Percent area stenosis by intravascular ultrasound was 57%. *Black arrow* points to internal elastic membrane, and *white arrow* to plaque mass.

shortened views of the LM trunk were obtained in the shallow left or right anterior oblique view with optimal caudal or cranial angulation, as necessary. All interventional procedures and ultrasound imaging were performed over an 0.014 inch coronary guidewire (Advanced Cardiovascular Systems, Mountain View, California).

The ultrasound device consists of a 20 MHz, 1.75 mm aperture, single-piezoelectric crystal transducer that is mechanically rotated within a 4.8Fr monorail, over-the-wire catheter at 1,800 rpm to provide 2-dimensional tomographic images (Boston Scientific Corporation, Watertown, Massachusetts). The images are displayed on a specially designed console (Diasonics, Inc., Milpitas, California). The intravascular ultrasound catheter was advanced over the wire distal to the lesion, and images were recorded on videotape as the catheter was withdrawn slowly through the lesion and LM trunk, and finally into the guiding catheter.

Ultrasound image analysis: Intravascular ultrasound images of the LM coronary artery were analyzed by 3 observers off-line using a Hewlett-Packard SONOS 1000 system (Andover, Massachusetts). In the image displaying the most severe LM stenosis, minimal lumen diameter, cross-sectional lumen area and cross-sectional area enclosed by the internal elastic lamina were quantitatively analyzed. Cross-sectional plaque area was calculated by subtracting lumen area from internal elastic lamina area. Percent area stenosis was determined by dividing plaque area by internal elastic lamina area. Morphologic characteristics such as plaque composition (hard vs soft) and topography (eccentric vs concentric) were evaluated as previously suggested.[7] Hard plaque was defined as vessel wall thickening with bright reflected echoes or distal acoustic shadowing consistent with the presence of calcium, or both. Lacking these characteristics, soft plaque was represented as less dense echoes of thickened vessel wall. Eccentric plaque was defined as atheroma involving <50% of the total circumference of the vessel, whereas concentric plaque involved >50% of the circumference.

Contrast angiography: Contrast angiography was performed with hand injections of nonionic contrast, and images were obtained at 30 frames/s in a 7-inch image intensifier mode. Two experienced angiographers, unaware of the ultrasound image interpretation, visually analyzed all images and noted whether the LM coronary artery appeared angiographically normal or abnormal. Images that were abnormal by visual examination were quantitatively analyzed. The worst view of the LM was

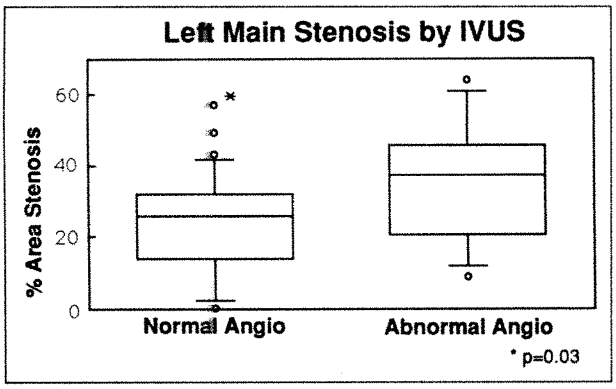

FIGURE 2. Percent area stenosis by intravascular ultrasound (IVUS) was significantly less in normal than abnormal angiographic (Angio) group. This figure depicts data in box plot. *Upper and lower edges of box* represent 75th and 25th percentiles, respectively, and *middle line,* the median. *Upper and lower bars* represent 90th and 10th percentiles, respectively, and *points* above or below 90th and 10th percentiles are plotted.

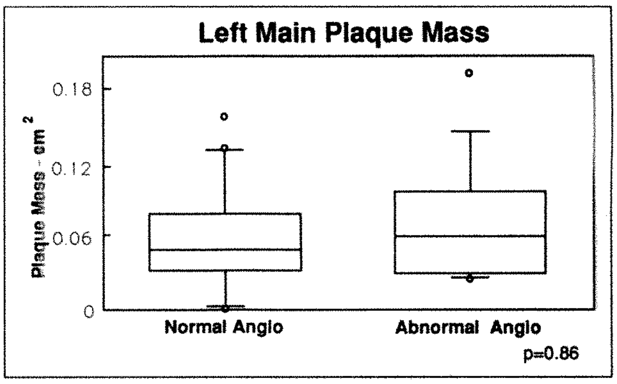

FIGURE 3. Plaque area in abnormal left main group was not significantly different from that in normal angiographic (Angio) group. This figure depicts data in box plot. *Upper and lower edges of box* represent 75th and 25th percentiles, respectively, and *middle line,* the median. *Upper and lower bars* represent 90th and 10th percentiles, respectively, and *points* above or below 90th and 10th percentiles are plotted.

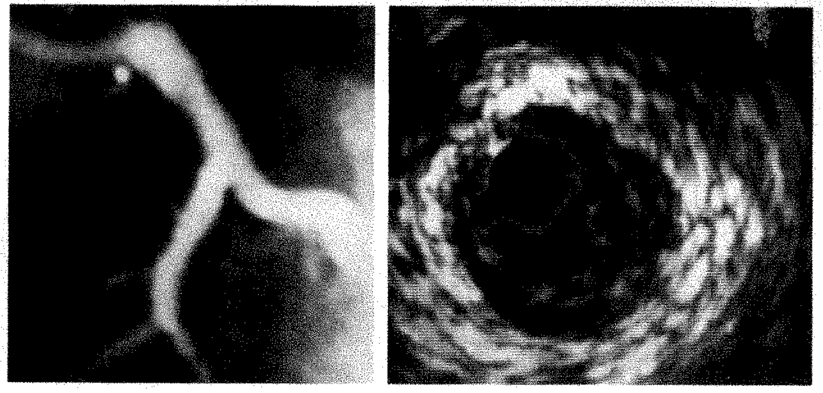

FIGURE 4. *Left,* cranial left anterior oblique coronary angiogram of patient with insignificant abnormality of distal left main trunk. By quantitative angiography, percent area stenosis was 34%. *Right,* corresponding intracoronary ultrasound image. Percent area stenosis by intravascular ultrasound was 59%

digitized and analyzed with a previously validated contour-detection algorithm.[11] Percent diameter stenosis and percent area stenosis were defined at the site and view where the coronary angiographic image displayed minimal LM diameter.

Statistical analysis: Continuous data are presented as median (25th, 75th percentile). The correlation between angiographic and intravascular ultrasonographic images was calculated with linear regression. For comparison of continuous variables between 2 groups, the nonparametric Mann-Whitney test was used.

RESULTS

Angiographically normal left main artery: LM angiograms were normal by visual interpretation in 27 patients. Intravascular ultrasound detected plaque in 24 of 27 patients (89%). Figure 1 is an example of a normal angiographic LM artery; however, by intracoronary ultrasound, there was a 57% area stenosis. In the angiographically normal group, the median percent area stenosis by intravascular ultrasound was 26% (14, 32%), which was less than the angiographically abnormal group's median of 37% (20, 46%) ($p = 0.03$) (Figure 2). However, the plaque area was not significantly different (normal 0.05 cm^2 [0.03, 0.08] vs abnormal 0.06 cm^2 [0.03, 0.1]; $p = 0.86$) (Figure 3). Three patients had >40% area stenosis, and 1 had >50%. Analysis of plaque composition revealed that 7 of 27 cases had hard plaque, and topographic analysis in this group found concentric plaque in 7 (26%) and eccentric plaque in 20 (74%).

Angiographically abnormal left main artery: In 11 patients, coronary angiography revealed abnormalities of the LM trunk. Intravascular ultrasound detected plaque in all 11 patients. Figure 4 shows an insignificant (37% area stenosis) LM lesion underestimated with quantitative angiography, which by intracoronary ultrasound was found to cause a 59% area stenosis with a plaque area of 0.10 cm^2.

In this group of patients, the plaque was eccentric in 9 and concentric in 1; it was predominantly hard in 3 and soft in 8. One patient had fluoroscopic LM calcification, and corresponding acoustic images revealed hard plaque and shadowing. Quantitative angiographic percent area stenosis was discordant from intracoronary ultrasound ($r = 0.12$; SEE 19%; $p = 0.72$) (Figure 5).

In a patient with angiographic distal LM disease (38% area stenosis), it was unclear from arteriography whether the obstruction was sufficiently severe to preclude the use of directional coronary atherectomy. In this patient, intravascular ultrasound confirmed that the percent area stenosis was only 37%, and consequently, left anterior descending directional atherectomy was chosen rather than balloon angioplasty.

DISCUSSION

Accurately evaluating the degree of LM coronary artery stenosis is of paramount importance.[12] Unfortunately, its correct diagnosis currently depends exclusively on selective coronary arteriography. Numerous studies over the past 2 decades demonstrated the limitations of angiographic imaging, particularly in the LM artery.[13] Fisher et al[3] analyzed 810 arteriograms from the Coronary Artery Surgery Study that were independently read by 2 angiographers. Measurements of the LM artery were the least reproducible of any coronary arterial segment analyzed. When 1 angiographer read a stenosis of ≥50%, a second one reported no lesion 18.6% of the time. In addition to being imprecise, LM imaging is also inaccurate. Isner et al[2] evaluated the accuracy of coro-

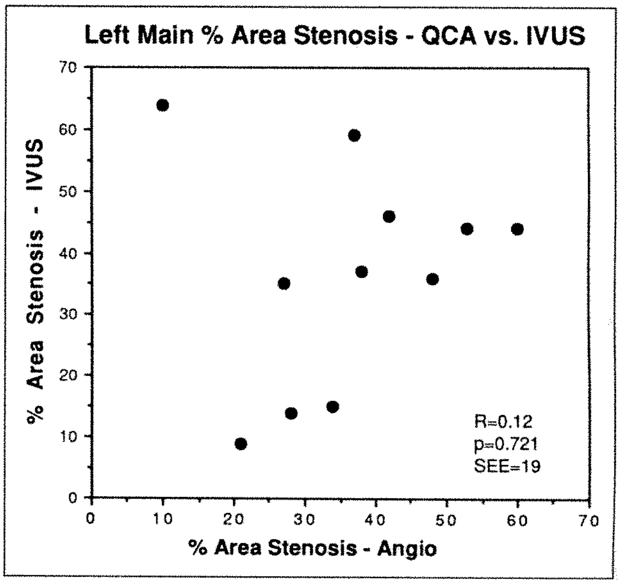

FIGURE 5. In patients with abnormal left main, there was no correlation between intravascular ultrasound (IVUS) and quantitative coronary angiographic (QCA) percent area stenoses. Angio = angiography.

nary angiography in detecting LM disease. They compared the degree of narrowing of the LM artery observed by angiography with histologic analysis at necropsy in 28 patients with symptomatic ischemia in whom angiography was performed within 40 days of death. In 46% of patients, at least 2 of 3 angiographers significantly underestimated the severity of LM stenosis. Six of 12 LM arteries narrowed by 76 to 100% in cross-sectional area were substantially underestimated by 2 of 3 angiographers.

The present study, using intracoronary ultrasound, confirms these pathologic observations. A very high percentage (89%) of patients with angiographically normal vessels had disease by ultrasound, and 4 of 27 had >40% area stenosis. Furthermore, the median plaque area by intravascular ultrasound was similar in angiographically normal and abnormal vessels. These findings are consistent with other in vivo investigations that have shown the superior sensitivity of intravascular ultrasound in peripheral and coronary arteries.[8,9,14,15]

In previous studies from our group, intravascular ultrasound was compared with digital angiography in 86 human peripheral arterial segments.[14] Intravascular ultrasound identified plaque in 24 sites, and 11 of these (46%) appeared normal by digital subtraction angiography. Intravascular and external high-frequency ultrasound, and angiography were compared in 29 peripheral vascular segments (superficial or common femoral arteries).[15] Intravascular ultrasound detected 15 plaques in these segments, and these were confirmed by external ultrasound, whereas angiography detected only 6 lesions. Several in vitro studies have shown intravascular ultrasound to be highly specific, with excellent correlations between histologic and ultrasound analyses of plaque distribution, thickness and shape.[4,16]

In the present study, there was no correlation in luminal dimensions between intravascular ultrasound and quantitative coronary angiography in the group with angiographically detectable disease. In vitro and in vivo peripheral arterial studies have, in contrast, found excellent correlations between the 2 imaging modalities with respect to lumen size.[5-8,14,15] The particularly poor correlation in the LM artery is likely due to the unique geometry of the LM trunk itself or to the generic limitations of silhouette angiography, or both. Because of its variable origin off the aorta, its inconsistent superior and inferior course, and variable length, obtaining adequate orthogonal views of the LM artery may be impossible. To overcome this problem, angiographic images were obtained in ≥2 views that minimized foreshortening. However, silhouette angiographic imaging cannot detect or underestimates diffuse, concentric plaque, because there is no reference segment for comparison.[17] Furthermore, recent studies showed that atherosclerotic arteries undergo compensatory enlargement. Because of the expanding circumference of the internal elastic membrane, the lumen area can be conserved as atheroma accumulates.[18,19] Thus, an atherosclerotic vessel with a conserved lumen area will appear angiographically normal. In contrast, by intravascular ultrasound, there can be significant percent area reduction, because the effect of plaque mass is negated by an enlarging internal elastic membrane. Another explanation for the poor correlation can be attributed to intravascular ultrasound itself. It has certain limitations that affect image quality, such as catheter eccentricity and beam divergence that can lead to errors in the quantitative determination of lumen area.

This study demonstrates the ubiquitous nature of LM atherosclerosis in patients undergoing interventional procedures. Because many coronary interventional devices are large and inflexible, the presence of LM disease by ultrasound can alter the device selected for percutaneous revascularization. Furthermore, this study suggests that intravascular ultrasound can be a useful adjunctive imaging method for evaluating LM coronary artery disease.

REFERENCES

1. Takaro T, Pifarre R, Fish R. Left main coronary artery disease. *Prog Cardiovasc Dis* 1985;28:229–234.

2. Isner JM, Kishel J, Kent KM, Ronan JA, Ross AM, Roberts WC. Accuracy of angiographic determination of left main coronary arterial narrowing: angiographic-histologic correlative analysis in 28 patients. *Circulation* 1981;63:1056–1064.

3. Fisher LD, Judkins MP, Lesperance J, Cameron A, Swaye P, Ryan T, Maynard C, Bourassa M, Kennedy JW, Gosselin A, Kemp H, Faxon D, Wexler L, Davis KB. Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). *Cathet Cardiovasc Diagn* 1982;8:565–575.

4. Pandian NG, Kreis A, Brockway B, Isner JM, Sacharoff A, Boleza E, Caro R, Muller D. Ultrasound angioscopy: real-time, two-dimensional, intraluminal ultrasound imaging of blood vessels. *Am J Cardiol* 1988;62:493–494.

5. Yock PG, Linker DT, Angelsen BAJ. Two-dimensional intravascular ultrasound: technical development and initial clinical experience. *J Am Soc Echo* 1989;2:296–304.

6. Pandian NG, Kreis A, Brockway B, Isner JM, Salem D, Sacharoff A, Boleza E, Caro R. Ultrasound angioscopy: feasibility and potential. *Echocardiography* 1989;6:1–7.

7. Gussenhoven EJ, Essed CE, Lancee CT, Mastik F, Frietman P, Van Egmond FC, Reiber J, Bosch H, Van Urk H, Roelandt J, Bom N. Arterial wall characteristics determined by intravascular ultrasound imaging: an in-vitro study. *J Am Coll Cardiol* 1989;14:947–952.

8. Tobis JM, Mallery JA, Gessert J, Griffith J, Mahon D, Bessen M, Moriuchi M, McLeay L, McRae M, Henry WL. Intravascular ultrasound cross-sectional arterial imaging before and after balloon angioplasty in vitro. *Circulation* 1989;80:873–882.

9. Davidson CJ, Sheikh KH, Kisslo KB, Phillips HR, Peter RH, Behar VS, Kong Y, Krucoff M, Ohman EM, Tcheng JE, Stack RS. Intracoronary ultrasound evaluation of interventional technologies. *Am J Cardiol* 1991;68:1305–1309.

10. Mallery JA, Tobis JM, Griffith J, Gessert J, McRae M, Moussabeck O, Bessen M, Moriuchi M, Henry WL. Assessment of normal and atherosclerotic arterial wall thickness with an intravascular ultrasound imaging catheter. *Am Heart J* 1989;19:1392–1401.

11. Fortin DF, Spero LA, Cusma JT, Santoro L, Burgess R, Bashore TM. Pitfalls in the determination of absolute dimensions using angiographic catheters as calibration devices in quantitative angiography. *Am J Cardiol* 1991;68:1176–1182.

12. Conley MJ, Ely RL, Kisslo J, Lee KL, McNeer JF, Rosati RA. The prognostic spectrum of left main stenosis. *Circulation* 1978;57:947–952.

13. Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DG, Kerber RE. Visual estimates of percent diameter coronary stenosis; "a battered gold standard." *J Am Coll Cardiol* 1988;11:882–885.

14. Davidson CJ, Sheikh KH, Harrison JK, Himmelstein SI, Leithe ME, Kisslo KB, Bashore TM. Intravascular ultrasonography versus digital subtraction angiography: a human in vivo comparison of vessel size and morphology. *J Am Coll Cardiol* 1990;16:633–636.

15. Sheikh KH, Davidson CJ, Kisslo KB, Harrison JK, Himmelstein SI, Kisslo J, Bashore TM. Comparison of intravascular ultrasound, external ultrasound and digital angiography for evaluation of peripheral artery dimensions and morphology. *Am J Cardiol* 1991;67:817–822.

16. Tobis JM, Mallery J, Mahon D, Lehmann K, Zalesky P, Griffith J, Gessert J, Moriuchi M, McRae M, Dwyer ML, Greep N, Henry WL. Intravascular ultrasound imaging of human coronary arteries in vivo. *Circulation* 1991;83:913–926.

17. Marcus ML, Harrison DG, White CW, McPherson DD, Wilson RF, Kerber RE. Assessing the physiologic significance of coronary obstructions in patients: importance of diffuse undetected atherosclerosis. *Prog Cardiovasc Dis* 1988;31:39–56.

18. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;316:1371–1375.

19. Stiel GM, Stiel LSG, Schofer J, Donath K, Mathey DG. Impact of compensatory enlargement of atherosclerotic coronary arteries on angiographic assessment of coronary artery disease. *Circulation* 1989;80:1603–1609.

Transient Myocardial Ischemia During Nifedipine Therapy in Stable Angina Pectoris, and Its Relation to Coronary Collateral Flow and Comparison with Metoprolol

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There are conflicting results concerning the anti-ischemic effect of nifedipine in patients with chronic stable angina. Therefore, the purpose of this study was to assess whether the anti-ischemic effect of nifedipine may be related to coronary collateral circulation. Forty-one patients with stable angina and coronary artery disease were randomized to a parallel double-blind study with nifedipine and metoprolol, and compared for effects on transient ischemic episodes during ambulatory electrocardiographic monitoring and exercise-induced ischemia. The effects were correlated to the presence of collateral circulation. In 17 patients, angiographically poor or no collateral flow was observed (group 1), and 24 had good collateral flow (group 2). Nifedipine was administered to 20 patients (8 in group 1, and 12 in group 2). In group 1, nifedipine reduced the frequency of total and asymptomatic ischemic episodes ($p <0.05$), whereas significant increases in both total ($p <0.05$) and silent ($p <0.01$) ischemia were observed in group 2. Exercise variables were slightly improved ($p =$ NS) during nifedipine therapy in group 1, and slightly worsened ($p =$ NS) in group 2. Reflex tachycardia was not observed at either the onset of transient ischemia out of the hospital or exercise-induced ischemia. This was in contrast with the effect in 21 patients treated with metoprolol (9 in group 1, and 12 in group 2) where significant reductions were observed in the frequency of both total ($p <0.01$) and silent ($p <0.01$) ischemia in both groups. Furthermore, a beneficial effect was observed on all exercise variables. Thus, the anti-ischemic effect of nifedipine appears to be influenced by the presence of coronary collateral flow, and increased ischemic activity may be due to a coronary steal phenomenon.

(Am J Cardiol 1993;71:177–183)

There is controversy concerning the anti-ischemic effect of the calcium antagonist nifedipine, because its reported effects on frequency of angina, ischemic variables during exercise testing and ambulatory monitoring vary considerably.[1–8] The pathophysiology of ischemic episodes during daily life appears to differ from myocardial ischemia induced during exercise testing,[9–11] because the heart rate in relation to transient ischemia out of the hospital is significantly less than that observed during exercise-induced ischemia, which suggests a reduction in myocardial oxygen supply as a major determinant of ambulatory ischemia with or without symptoms. Therefore, the coronary vasodilator effect of nifedipine should be beneficial, resulting in increased coronary flow and myocardial oxygen supply.

This study assesses the variable anti-ischemic effect of nifedipine, using the hypothesis that its efficacy may be related to the presence of coronary collateral flow, which could be associated with a coronary steal phenomenon. Furthermore, a double-blind comparison was performed with metoprolol, a β-adrenoceptor blocking drug without known coronary vasodilator effect, to assess if the presence of coronary collateral flow is of importance for the anti-ischemic response to different therapies.

METHODS

Patient cohort and protocol: The study comprised 41 patients (aged <70 years) with chronic stable angina for ≥6 months and without a myocardial infarction in the preceeding 3 months. Patients with unstable angina, overt heart failure and severe hypertension were excluded from the study; those with bundle branch block, receiving any medication that could influence ST-segment evaluation, with gross left ventricular hypertrophy or severe valvular heart disease, or without sinus rhythm were excluded, as well.

After entering the study, all antianginal medication was withdrawn, and patients were administered placebo in a single-blind manner for 1 week, allowing only sublingual nitrates for relief of anginal pain, but not for prophylactic use. During the placebo period, coronary arteriography was performed in all patients, and a symptom-limited, maximal exercise test and ambulatory monitoring were performed at the end of the period. Patients then began a 2-week, double-blind, parallel study with nifedipine and metoprolol. During this period, patients were randomized to receive either nifedipine (10 mg, 3

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TABLE I Previous Myocardial Infarction, Type, Localization and Hemodynamic Variables

Nifedipine					Metoprolol				
Pt. No.	MI Type	Localization	EF (%)	LVEDP (mm Hg)	Pt. No.	MI Type	Localization	EF (%)	LVEDP (mm Hg)
Group 1									
5	Multiple	Multiple	71	8	3	—	—	74	9
12	—	—	79	6	7	Trans.	Ant.	57	13
15	Multiple	Multiple	67	16	9	Trans.	Ant.	56	6
17	—	—	40	24	13	Trans.	Inf.	59	3
21	Trans.	Ant.	64	20	18	Trans.	Ant.	52	5
26	Trans.	Inf.	42	18	25	—	—	79	14
29	—	—	73	7	28	—	—	80	6
34	Sub.	Inf.	87	6	30	Trans.	Ant.	87	6
					40	—	—	73	12
Group 2									
1	Trans.	Ant.	59	11	4	Trans.	Ant.	56	9
2	Trans.	Inf.	48	8	10	—	—	74	6
6	Trans.	Inf.	71	8	11	Trans.	Ant.	67	16
8	Sub.	Ant.	42	12	14	Trans.	Ant.	61	16
16	Multiple	Multiple	21	15	19	Trans.	Inf.	52	5
23	Trans.	Ant.	41	16	20	Sub.	Inf.	53	12
24	Trans.	Inf.	79	14	22	Sub.	Ant.	68	24
27	Trans.	Inf.	80	6	32	—	—	83	14
31	Multiple	Multiple	54	8	35	Trans.	Ant.	47	9
33	—	—	86	12	36	Trans.	Ant.	56	4
37	Trans.	Inf.	80	2	38	Multiple	Multiple	37	17
39	Trans.	Inf.	62	8	41	—	—	80	2

Ant. = anterior; EF = ejection fraction; Inf. = inferior; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; Sub. = subendocardial; Trans. = transmural.

times daily the first week and 20 mg, 3 times daily the second week) or metoprolol (50 mg twice daily the first week, and 100 mg twice daily the second week). The design with 2 dose levels was selected to avoid drug-related side effects. All assessments were performed at the end of both the placebo period and the second week of active treatment. Patients did not receive any other concomitant medication that could affect ischemic activity. The effects on total ischemic activity compared with placebo have been reported elsewhere.[5] All patients gave informed consent before inclusion, and the study was approved by the local ethical committee.

Coronary angiography: Selective coronary angiography was performed in standard projections and evaluated blindly by an experienced investigator. For each patient, the number and localization of coronary artery stenoses were determined. Coronary stenoses were estimated as a percentage of luminal narrowing based on diameter reduction, and narrowing >75% was considered significant.

Coronary collateral circulation was classified according to previous description.[12] Patients were divided into the following 2 groups: group 1, no or poor collateral flow, defined as <50% opacity of the distal coronary artery receiving collateral flow compared with the segment proximal to the stenosed or obstructed vessel; and group 2, good collateral flow, where the opacity of the distal segment of the coronary artery was ≥50% of the proximal segment. If >1 coronary artery was collateralized, the patient was assessed according to the best collateral flow. Before coronary angiography, left ventriculography was performed with measurement of ejection fraction and left ventricular end-diastolic pressure.

Ambulatory monitoring: Ambulatory monitoring was performed for 36 hours at the end of both the placebo period and active treatment, using a calibrated, amplitude-modulated 2-channel tape recorder (Tracker Reynolds). Transient ST-segment depression was defined as >1 mm of horizontal or downsloping ST-segment depression 80 ms after the J point, and ST-segment elevation as >1 mm of ST-segment elevation at the J point. Each episode had to last ≥1 minute, and ≥2 minutes of normalization of the ST segment were required to define 2 separate episodes. The method has been described in detail elsewhere.[5] The number of symptomatic and silent ischemic episodes, their duration and heart rate at the onset of ischemia were noted for each tape.

Exercise testing: A maximal, symptom-limited, bicycle exercise test was performed at the end of both the placebo period and active treatment. A 12-lead, precordial mapping system was used to enhance the detection of ST-segment changes.[13] The same criteria for ST-segment change was used as that during ambulatory monitoring. For each exercise test, the maximal exercise load was noted, as well as the time to ST-segment change and angina, and heart rate at the onset of ST-segment change and angina. Blood pressure was measured at rest, during each level of work load, at maximal work load and during the recovery phase.

Statistical analysis: Data are expressed as mean ± SD, and 2-tailed p values <0.05 were considered significant. Data obtained during ambulatory monitoring were analyzed by nonparametric statistics, with the Wilcoxon signed-rank test for within-group comparisons and the Mann-Whitney test for between-group comparisons.

TABLE II Coronary Pathoanatomy and Occurrence of Coronary Collateral Flow*

Pt. No.	LM	LAD Prox.	LAD Distal	CX Prox.	CX Distal	RCA Prox.	RCA Distal	Collateral Flow
1	—	—	—	100	—	50	90	Good
2	—	100	—	50	—	<50	—	Good
3	—	50	—	—	—	90	100	Bad
4	—	100	—	50	—	90	—	Good
5	—	90	100	—	—	90	100	No
6	—	100	—	<50	—	<50	<50	Good
7	—	75	—	<50	—	<50	—	No
8	—	100	—	100	—	<50	—	Good
9	—	75	—	50	90	75	90	No
10	—	100	—	—	—	—	—	Good
11	—	100	—	<50	—	—	—	Good
12	—	50	—	<50	—	75	—	No
13	—	—	—	<50	—	75	—	No
14	—	100	—	—	—	—	—	Good
15	—	100	—	50	75	100	—	Bad
16	—	100	—	<50	—	75	—	Good
17	—	90	—	90	—	50	—	No
18	—	100	—	—	—	90	—	No
19	—	90	—	100	—	75	—	Good
20	<50	100	—	50	90	100	—	Good
21	—	90	90	—	—	—	—	No
22	—	100	—	—	—	—	—	Good
23	50	90	100	50	—	<50	—	Good
24	—	100	—	100	—	90	—	Good
25	<50	90	75	75	—	90	75	No
26	—	50	—	90	—	50	—	No
27	—	90	—	—	—	100	—	Good
28	—	90	—	90	—	75	—	No
29	75	90	—	<50	—	—	—	No
30	—	75	—	—	—	75	—	No
31	50	75	—	<50	—	100	—	Good
32	—	75	50	100	—	100	—	Good
33	—	100	—	—	—	90	—	Good
34	—	90	—	90	—	90	—	No
35	—	—	—	50	100	75	—	Good
36	—	100	—	—	—	—	—	Good
37	—	—	—	50	—	100	—	Good
38	—	100	—	<50	—	50	—	Good
39	—	75	—	75	—	90	100	Good
40	—	—	—	—	—	75	—	No
41	—	100	—	<50	—	75	—	Good

*Values equal diameter reduction (%).
CX = left circumflex coronary artery; LAD = left anterior descending coronary artery; LM = left main stem; Prox. = proximal; RCA = right coronary artery.

Furthermore, variables obtained during ambulatory monitoring were calculated for each hour to adjust for different baselines values. Exercise variables were tested with multivariate analyses of variance and unpaired *t* test.

RESULTS

The study comprised 40 men and 1 woman. The mean age was 55 ± 7 years, systolic blood pressure 133 ± 17 mm Hg and diastolic blood pressure 88 ± 12 mm Hg, and 30 patients had a previous myocardial infarction (Table I). There were no significant differences between patients randomized to nifedipine and metoprolol.

Coronary anatomy: All 41 patients had coronary artery stenosis of $>75\%$ in ≥ 1 major coronary artery. In 17 angiograms (group 1), collateral flow was either absent or poor, whereas 24 patients (group 2) had good collateral flow (Table II). Of 17 patients in group 1, 8 received nifedipine and 9 metoprolol, and in group 2, 12

TABLE III Coronary Angiographic Diameter Reduction in Patients Randomized to Nifedipine or Metoprolol*

	Nifedipine	Metoprolol
LAD		
100%	9	8
90–99%	5	5
75–89%	2	3
<75%	3	4
CX		
100%	3	2
90–99%	3	1
75–89%	1	1
<75%	4	4
RCA		
100%	3	3
90–99%	6	3
75–89%	3	7
<75%	2	2

*Values equal number of coronary vessels.
Abbreviations as in Table II.

TABLE IV Frequency and Duration of Total and Silent Ischemia in Individual Patients with No or Bad Collateral Flow (group 1) During Placebo and Nifedipine/Metoprolol Therapy

	Placebo				Nifedipine			
Pt. No.	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)
5	8	6	67	58	5	3	59	27
12	7	6	80	48	4	2	55	45
15	0	0	0	0	0	0	0	0
17	7	5	102	96	4	2	98	32
21	10	8	124	80	8	6	80	66
26	7	4	109	53	5	3	97	63
29	3	2	63	47	3	3	63	63
34	4	3	64	58	4	2	90	80

	Placebo				Metoprolol			
Pt. No.	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)
3	9	7	135	61	5	3	37	21
7	1	0	3	0	3	3	30	30
9	7	5	25	19	2	1	9	6
13	0	0	0	0	0	0	0	0
18	2	1	40	37	1	1	5	5
25	6	6	87	87	2	1	13	7
28	2	1	39	26	1	1	18	18
30	4	2	17	9	0	0	0	0
40	4	3	43	35	2	2	38	38

SI = silent ischemia; TI = total ischemia.

patients received nifedipine and 12 metoprolol. The angiographic diameter reductions in the proximal part of the left anterior descending, left circumflex and right coronary arteries for patients subsequently randomized to nifedipine and metoprolol are listed in Table III. There were no differences between the 2 treatment groups.

Data for ejection fraction and left ventricular end-diastolic pressure are listed in Table I. Ejection fraction was 62 ± 17% in the nifedipine group, and 65 ± 13% in the metoprolol group (p = NS), and the corresponding figures for left ventricular end-diastolic pressure were 11 ± 5 and 10 ± 6 mm Hg (p = NS), respectively.

Ambulatory monitoring: In all, ambulatory monitoring was performed for 2,755 hours, and 352 ischemic episodes were observed (275 [78%] asymptomatic). The total duration of ischemia was 4,365 minutes, and 3,090 (71%) were silent.

EFFECTS OF NIFEDIPINE: A significant decrease in ischemic activity was observed for both the total number of

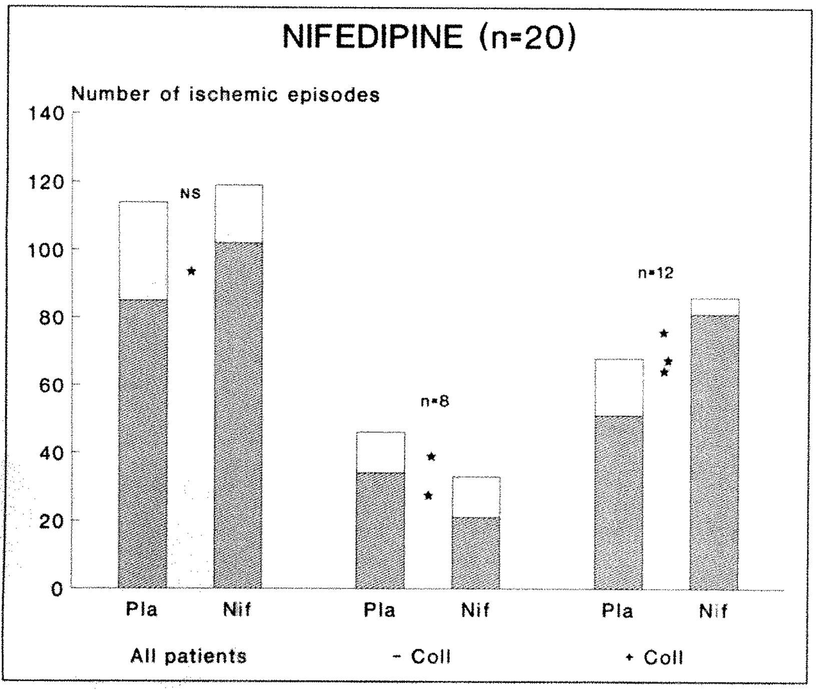

FIGURE 1. Effects of placebo (Pla) and nifedipine (Nif) on total *(whole bars)* and silent *(hatched bars)* ischemia in patients with no or poor (– Coll) or good (+ Coll) collateral flow. *p <0.05; **p <0.01.

ischemic episodes (46 with placebo vs 33 with nifedipine; p <0.05) and asymptomatic ischemia (34 with placebo vs 21 with nifedipine; p <0.05) in group 1. In contrast, a significant increase was observed in total ischemic activity (68 episodes with placebo vs 86 with nifedipine; p <0.05) and asymptomatic ischemia (51 with placebo vs 81 with nifedipine; p <0.01) in group 2 (Figure 1). A significant increase was observed in total

TABLE V Frequency and Duration of Total and Silent Ischemia in Individual Patients with Good Collateral Flow (group 2) During Placebo and Nifedipine/Metoprolol Therapy

	Placebo				Nifedipine			
Pt. No.	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)
1	11	8	105	43	9	8	101	37
2	3	3	51	51	9	9	19	19
6	4	3	50	31	7	6	61	23
8	11	8	131	101	12	12	284	284
16	2	1	21	12	5	5	62	62
23	5	4	112	57	8	7	39	15
24	8	6	49	39	6	6	59	59
27	5	3	11	20	1	1	44	44
31	2	2	8	8	1	0	10	0
33	2	2	102	102	7	6	51	17
37	10	8	92	70	12	12	220	220
39	5	3	88	24	9	9	92	92

	Placebo				Metoprolol			
Pt. No.	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)	No. of TI	No. of SI	Duration of TI (min)	Duration of SI (min)
4	10	5	96	23	10	7	84	29
10	0	0	0	0	1	1	10	10
11	1	1	5	5	0	0	0	0
14	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0
20	7	5	106	34	2	2	26	26
22	10	8	108	62	3	3	29	29
32	5	4	61	30	2	2	51	51
35	5	3	41	12	1	1	11	11
36	4	3	102	67	1	1	16	16
38	0	0	0	0	0	0	0	0
41	5	5	60	60	1	0	7	0

Abbreviations as in Table IV.

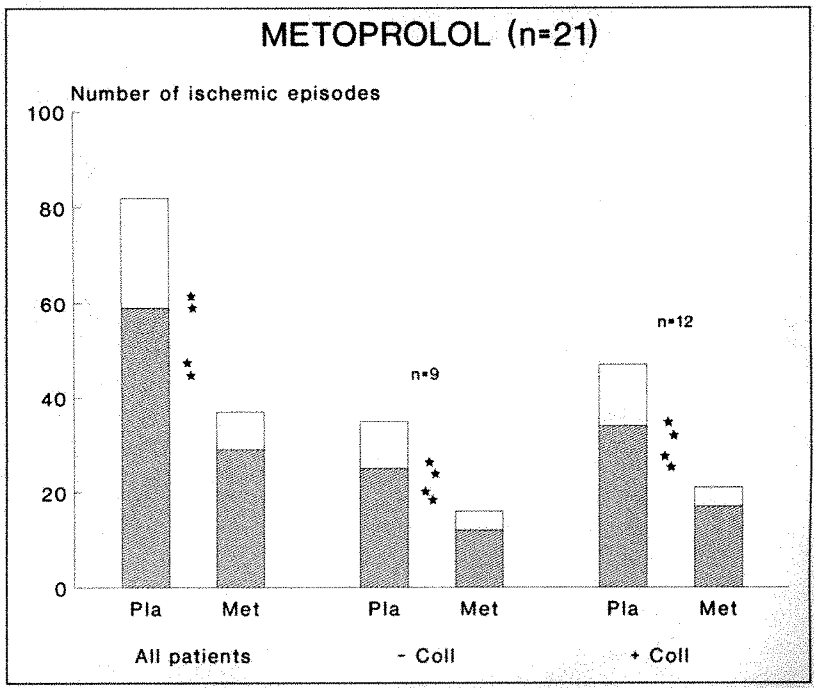

FIGURE 2. Effects of placebo (Pla) and metoprolol (Met) on total *(whole bars)* and silent *(hatched bars)* ischemia in patients with no or poor (– Coll) or good (+ Coll) collateral flow. **p <0.01.

TABLE VI Exercise Variables During Therapy with Placebo, Nifedipine and Metoprolol in Relation to Coronary Collateral Flow

		Nifedipine				Metoprolol		
	Placebo (n = 20)	All Pts. (n = 20)	Group 1 (n = 8)	Group 2 (n = 12)	Placebo (n = 21)	All Pts. (n = 21)	Group 1 (n = 9)	Group 2 (n = 12)
Max. ex. load (W)	93 ± 40	92 ± 30	94 ± 32	90 ± 38	92 ± 38	121 ± 46*	121 ± 43*	122 ± 47*
Time to ST-segment change (min)	6 ± 4	7 ± 3	7 ± 4	5 ± 3	6 ± 4	10 ± 3†	10 ± 3†	10 ± 3†
Time to angina (min)	7 ± 3	8 ± 4	9 ± 3	6 ± 4	7 ± 3	12 ± 4†	11 ± 5†	12 ± 4†
HR/ST (beats/min)	116 ± 20	120 ± 21	119 ± 23	120 ± 19	115 ± 24	96 ± 10‡	95 ± 12‡	96 ± 13‡
HR/pain (beats/min)	118 ± 17	121 ± 18	120 ± 25	122 ± 18	120 ± 19	97 ± 12‡	98 ± 9‡	97 ± 14‡

*p <0.05; †p <0.01, ‡p <0.001 compared with placebo.
Data are expressed as mean ± SD.
ex. = exercise; HR/pain = heart rate at onset of angina; HR/ST = heart rate at onset of ST-segment change; Max. = maximal.

duration of both ischemia (p <0.05) and silent ischemia (p <0.05) in group 2, whereas no significant effect was observed in group 1. Individual data for frequency and duration of total and silent ischemia are listed in Tables IV and V, and the tables are organized according to medication and presence of collateral flow. Heart rate at the onset of ischemia was not significantly changed during nifedipine therapy compared with during placebo treatment (102 ± 13 vs 99 ± 14 beats/min; p = NS), and there were no differences in heart rate between groups 1 and 2.

EFFECTS OF METOPROLOL: According to coronary anatomy, the reduction in frequency of ischemic activity for group 1 was from 35 to 16 for total ischemia and from 25 to 12 for silent ischemia (p <0.01); in group 2, the corresponding values for total ischemia were 47 to 21 and for asymptomatic ischemia 34 to 17 (p <0.01) (Figure 2). The duration of symptomatic and silent ischemia was also reduced (p <0.01). This reduction was independent of the presence of coronary collateral flow. Individual data for frequency and duration of total and silent ischemia are listed in Tables IV and V. Heart rate at the onset of ischemia was significantly reduced during metoprolol treatment compared with during placebo therapy (78 ± 10 vs 99 ± 14 beats/min; p <0.01), and the reduction in heart rate was the same for groups 1 and 2.

Exercise testing: EFFECTS OF NIFEDIPINE AND METOPROLOL: In patients with poor or no collateral flow, treatment with nifedipine induced a slight improvement (p = NS) in exercise variables, whereas a tendency toward reduction (p = NS) in the same variables was observed in patients with good collateral flow; both groups were compared with the same group of patients during placebo treatment. During nifedipine therapy, no change in heart rate was found, whereas a significant reduction in heart rate was observed during metoprolol therapy (Table VI).

Resting systolic blood pressure at the end of the placebo period was 132 ± 17 mm Hg for the nifedipine group and 134 ± 24 for the metoprolol group (p = NS). The corresponding figures at the end of active therapy were 128 ± 19 and 129 ± 22 mm Hg (p = NS), respectively. The values at maximal exercise were 173 ± 24 and 175 ± 28 mm Hg (p = NS), respectively, during placebo, and 167 ± 24 and 165 ± 36 mm Hg (p = NS), respectively, during active therapy. There were no differences between groups 1 and 2.

DISCUSSION

Coronary collateral flow appears to be a determinant of the anti-ischemic effect of nifedipine during out-of-hospital ischemia. Patients with or without poor collateral flow had a significant benefit from nifedipine therapy, with a reduction in both symptomatic and asymptomatic ischemia during daily life, and furthermore, a tendency toward improvement was observed in exercise variables. These observations correspond well with the anti-ischemic properties of nifedipine, with reduction of afterload, coronary vasodilatation and a metabolic effect on the myocardium.[14,15]

This was in contrast to the effect of nifedipine in patients with good collateral flow, where an increase in ischemic activity was found during daily life, with a marked increase in silent ischemia. Exercise variables showed the same tendency (p = NS). The absence of significance during exercise testing could be related to the relatively small number of patients or to differences in the pathophysiology of ischemia, where collateral circulation may be of more importance during ambulatory than exercise-induced ischemia, where flow-limiting coronary stenosis may have the major role. In other studies, the absence of an anti-ischemic effect of nifedipine has been ascribed to reflex tachycardia,[16,17] but in this study, no increase in heart rate was observed at the onset of ischemia out of the hospital or during exercise testing. The effect on blood pressure was the same during therapy with nifedipine and metoprolol. The dose of nifedipine was selected based on ordinary clinical use and was not individualized for each patient,[1,6,18] and even with a higher or lower dose, there have been nonresponders to therapy.[8,19]

This study is in accordance with that of Schulz et al,[19] who found that the anti-ischemic effect of nifedipine, assessed by exercise testing, was related to the presence of collateral vessels, and a coronary steal phenomenon through collaterals was suggested. We have expanded this observation to include the anti-ischemic effect of nifedipine during daily life. This steal phenomenon may induce myocardial ischemia by reducing coronary resistance and directing flow from poststenotic, underperfused areas to normally perfused myocardium. Coronary steal has also been described for dipyridamole, which is another arteriolar vasodilator.[20,21] This may indicate that coronary steal can occur with other arteriolar vasodilators. The relation between coronary anatomy and the anti-ischemic effect of nifedipine may explain the complexity of results from different studies in which nifedipine has had a beneficial effect on chronic stable coronary artery disease,[2,6] whereas other studies have found an absence of effect and even an increase in ischemic burden.[5]

Increased morbidity and mortality have been described during therapy with dihydropyridine calcium antagonists (nifedipine and nisoldipine) in patients with stable angina,[22] acute or threatened infarction,[23] or unstable angina.[24] This effect of dihydropyridine calcium antagonists has been described as pro-ischemia,[25] and the present study indicates that this could be mediated through a coronary steal.

Metoprolol produced a highly significant reduction in symptomatic, asymptomatic and exercise-induced myocardial ischemia, which was independent of coronary anatomy. Thus, coronary collateral circulation does not appear to be an independent factor for the anti-ischemic effect of various therapies.

This study has certain limitations. First, the number of ischemic episodes in patients randomized to nifedipine was greater (114) than in those with metoprolol (82). This difference appears to be based on a greater number of patients in the metoprolol group without ambulatory ischemia during placebo treatment. These patients remained without ischemia, and the reduction in ischemic activity by metoprolol was achieved in fewer patients. Second, the proposal of a coronary steal phenomenon is based on the medical effect in different groups of patients with or without collateral circulation and not on flow measurement in the coronary arteries.

Clinical implications: This study indicates that nifedipine may induce a coronary steal phenomenon in patients with significant coronary collateral flow, not only during exercise-induced ischemia, but also during symptomatic and asymptomatic ischemia out of the hospital. Therefore, the anti-ischemic effect of nifedipine in patients with chronic stable angina may be unpredictable if the coronary anatomy is not known. However, metoprolol may be used without knowledge of coronary anatomy.

REFERENCES

1. Uusitalo A, Arstila M, Bae EA, Härkönen R, Keyriläinen O, Rytkönen U, Schelderup-Mathiesen PM, Wendelin A. Metoprolol, nifedipine and the combination in stable effort angina pectoris. *Am J Cardiol* 1986;57:733–737.

2. Fox KM, Deanfield JE, Selwyn AP, Krikler S, Wright CA. Treatment of chronic stable angina pectoris with nifedipine. In: Kaltenbach M, Neufeld HN, eds. Fifth International Nifedipine Symposium. Amsterdam: Exerpta Medica, 1982:197–204.

3. Frishman WH, Charlap S, Kimmel B, Goldberger J, Phillippides G, Klein N. Hemodynamic effects of nifedipine during upright exercise in stable angina pectoris and either normal or severely impaired left ventricular function. *Am J Cardiol* 1986;57:22D–29D.

4. Bala Subramanian V, Bowles MJ, Khurmi NS, Davies AB, Raftery EB. Randomized double-blind comparison of verapamil and nifedipine in chronic stable angina. *Am J Cardiol* 1982;50:696–703.

5. Egstrup K. Randomized double-blind comparison of metoprolol, nifedipine and their combination in chronic stable angina: effects on total ischemic activity and heart rate at onset of ischemia. *Am Heart J* 1988;116:971–978.

6. Lynch P, Dargie H, Krikler S, Krikler D. Objective assessment of antianginal treatment: a double-blind comparison of propranolol, nifedipine and their combination. *Br Heart J* 1980;2:184–187.

7. Rizzo P, Scrutinio D, Mangini SG, Lagioia R, de Toma L. Randomized placebo-controlled comparative study of nifedipine, verapamil and isosorbide dinitrate in the treatment of angina at rest. *Eur Heart J* 1986;7:67–76.

8. Specchia G, de Servi S, Falcone C, Angoli L, Gavazzi A, Bramucci E, Mussini A, Ferrario M, Salermo J, Montemartini C. Effects of nifedipine on coronary hemodynamic findings during exercise in patients with stable exertional angina. *Circulation* 1983;68:1035–1043.

9. Egstrup K. The sensitivity of the symptom angina pectoris as a marker of transient myocardial ischaemia in chronic stable angina pectoris. *Acta Med Scand* 1987;222:301–306.

10. Deanfield JE, Selwyn AP, Chierchia S, Maseri A, Ribeiro D, Krikler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina; its relation to symptoms and heart rate changes. *Lancet* 1984;2:1001–1005.

11. Egstrup K. Transient myocardial ischaemia during ambulatory monitoring out of hospital in patients with chronic stable angina pectoris. *Acta Med Scand* 1988;224:311–318.

12. Elayda MA, Mathur VS, Hall RJ, Massumi GA, Garcia E, de Castro CM. Collateral circulation in coronary artery disease. *Am J Cardiol* 1985;55:58–60.

13. Egstrup K. The relationship between ST-segment deviation projected to the front of the chest during exercise and simultaneous Holter-monitoring. *Eur Heart J* 1988;9:412–419.

14. Serruys PW, Hoogkondt TEH, Reiber JHC, Slager C, Brower RW, Hugenholz PG. Influence of intracoronary nifedipine on left ventricular function, coronary vasomobility and myocardial oxygen consumption. *Br Heart J* 1983;49: 427–441.

15. Kaltenbach A, Schulz W, Kober G. Effects of nifedipine after intravenous and intracoronary administration. *Am J Cardiol* 1979;44:832–837.

16. Bolognesi R, Cucchini F, Manca C, Ferrari R. Effects of verapamil and nifedipine on rate of left ventricular relaxation in coronary arterial disease patients. *Int J Cardiol* 1987;14:333–341.

17. Shen WF, Roubin GS, Choong CY, Hutton BF, Harris PJ, Fletcher PJ, Kelly DT. Left ventricular response to exercise in coronary artery disease: relation to myocardial ischaemia and effects of nifedipine. *Eur Heart J* 1985;6:1025–1031.

18. Quyyumi AA, Crake T, Wright CM, Mockus LJ, Fox KM. Medical treatment of patients with severe exertional and rest angina: double-blind comparison of beta-blocker, calcium antagonist, and nitrate. *Br Heart J* 1987;57:505–511.

19. Schulz W, Jost S, Kober G, Kaltenbach M. Relation of antianginal efficacy of nifedipine to degree of coronary arterial narrowing and to presence of coronary collateral vessels. *Am J Cardiol* 1985;55:26–32.

20. Becker LC. Conditions for vasodilator induced coronary steal in experimental myocardial ischemia. *Circulation* 1978;57:1103–1110.

21. Fam WM, McGregor M. Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Circ Res* 1964;15:355–365.

22. Thadani U, Zellner SR, Glasser S, Bittar N, Montoro R, Miller AB, Chaitman B, Schulman P, Stahl A, DiBianco R, Bray J, Means WE, Morledge J, and Co-investigators. Double-blind, dose-response, placebo-controlled multicenter study of nisoldipine. *Circulation* 1991;84:2398–2408.

23. Muller JE, Morrison J, Stone PH, Rude RE, Rosner B, Roberts R, Pearle DL, Turi ZG, Schneider JF, Serfas DH, Tate C, Scheiner E, Sobel BE, Hennekens CH, Braunwald E. Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. *Circulation* 1984;69:740–747.

24. Report of the Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group. Early treatment of unstable angina in the coronary care unit: a randomized, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. *Br Heart J* 1986;56:400–413.

25. Waters D. Proischemic complications of dihydropyridine calcium channel blockers. *Circulation* 1991;84:2598–2600.

Comparison of Two Mechanical Ultrasound Devices With and Without Echogenic Contrast Dye

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To evaluate the impact and limitations of intracoronary ultrasound, 64 segments of 13 isolated coronary arteries were examined and 2 mechanical devices (device A, 30 MHz 5Fr [CVIS] and device B, 20 MHz 4.8Fr [Diasonics/Boston Scientific] were compared with the corresponding histologic specimens. Luminal dimensions were assessed with and without echogenic contrast dye (Laevovist®, Schering AG, Germany). After application of contrast dye, correlation of luminal area between histology and ultrasound was improved from $r = 0.62$ to $r = 0.77$ (device B; $p < 0.05$) and from $r = 0.82$ to $r = 0.88$ (device A; p = NS). Low accuracy of lumen measurements in segments <2.5 mm could be improved by application of contrast dye. The number of quadrants in which wall thickness measurements were impossible was significantly higher for device B ($n = 56$; 22%) than for device A ($n = 28$; 11%); $p < 0.01$. This may be due to the different ringdown diameters of both systems (B, 2.6 mm; A, 2.0 mm; $p < 0.0001$). In assessing wall thickness only in segments of >2.5 mm, a reliable correlation between ultrasound and histology was found (A, $r = 0.80$; B, $r = 0.60$). Sensitivity of plaque ($n = 51$) detection was lower for device B (63%) than for device A (82%, $p < 0.05$), and measurements correlated with histology only for device A. There are considerable differences in the accuracy of ultrasound measurements between mechanical systems. Nevertheless, additional application of contrast dye can improve accuracy of luminal measurements, especially in smaller vessels.

(Am J Cardiol 1993;71:184–191)

Catheter-based, coronary imaging by intravascular ultrasound has recently been introduced as a new technology in the assessment of coronary artery disease.[1–17] However, the experience with intracoronary ultrasound for diagnostic evaluation is limited.[7,8,10] Furthermore, there is an obvious lack of experimental data with regard to correlation between the ultrasound image and the microscopic anatomy of the human coronary artery.[11,18] Currently, several mechanical intravascular ultrasound devices using either a rotating transducer or a rotating mirror at the tip of the catheter are commercially available. However, no systematic comparison of these different technologies has been analyzed in in vitro studies. The results of transthoracic and transesophageal studies have demonstrated that echogenic contrast dye can improve image quality and provide higher accuracy of left and right ventricular measurements. Thus, it could be expected that the application of contrast dye would have an impact on the accuracy of lumen measurements of coronary arteries. The current study was designed to address these questions in an in vitro study in postmortem human coronary arteries comparing the ultrasound images with the histology of the corresponding segment. The aim of the study was to analyze the accuracy of intravascular ultrasound for determination of atherosclerotic plaque, lumen area and diameter and wall thickness, to compare intravascular imaging of 2 different mechanical ultrasound devices (mirror- versus transducer-rotating systems), and to evaluate the impact of echogenic contrast dye on the accuracy of measurements of lumen and luminal borders of coronary arteries.

METHODS

Ultrasound transducer: Two commercially available mechanical ultrasound imaging systems were used in this study: a 30 MHz transducer mounted on the tip of a 5Fr catheter (CVIS) and a 20 MHz transducer on the tip of 4.8Fr catheter (Boston Scientific/Diasonics). The principle of the first system is a rotating mirror (up to 1,500 rpm) reflecting the ultrasound beam emitted by an ultrasound crystal located at the tip of the catheter. The second system has a rotating ultrasound transmitting transducer (500 rpm).

Material: Ultrasound was performed using postmortem coronary arteries of 9 patients (8 men and 1 woman, aged 68 ± 11 years [mean ± SD, range 54 to 86]). Arterial specimens were collected during autopsy, and were studied fresh, without fixation within 6 hours after

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TABLE I Impact of Contrast Dye on the Accuracy of Lumen Measurements by Intravascular Ultrasound

No. of Lumen Area Measurements Possible Without Contrast Dye	Measurements Not Identical With and Without Contrast Dye	Deviation of Measurements With and Without Contrast Dye > 15%	From These: Contrast Dye Reduces Deviation Between Ultrasound and Histology	Measurements Only Possible After Contrast Dye
Rotating mirror (n = 62)	48% (n = 30)	16% (n = 10)	100% (10 of 10)	3%* (n = 2)
Rotating probe (n = 44)	77% (n = 34)	32% (n = 14)	100% (14 of 14)	16%* (n = 10)
	p = NS	p = NS		p < 0.05

*All vessels in this group had a lumen diameter ≤ 2.5 mm. With both devices, lumen and area measurements were possible in all 64 segments after application of contrast dye.

necropsy. The arteries were isolated sparing the adventitia and surrounding soft tissue to simulate in situ conditions. Side branches were tied off with sutures. Afterwards, the vessels were mounted on a special device (Figure 1) and perfused by physiologic saline solution. Intraluminal pressure was maintained constant at 70 mm Hg. Thus, 64 segments of 13 coronary arteries were visualized by 2 different mechanical ultrasound devices and compared with the respective histologic specimen.

Ultrasound imaging: The intravascular ultrasound catheter was inserted and aligned coaxially to the arterial segment. The total arrangement (Figure 1) was then immersed in a physiologic saline bath that was kept at room temperature. Images were then obtained at 0.5 cm intervals along the entire length of the artery. Gain, contrast and other parameters of pre- and postprocessing were adjusted for each image to provide optimal image quality. The position of the ultrasound catheter was marked within the surrounding soft tissue by needles for each measuring site, thus allowing the exact circular and longitudinal orientation.

Histology: After the ultrasound imaging procedure, arteries were pressure (70 mm Hg) perfusion-fixed in 10% neutral-buffered formalin, and 24 hours later placed in a standard decalcification solution. After embedding (paraffin), histologic sections were taken at the sites previously marked by needles. Before this procedure, the arteries were marked with India ink at the place where the reference needle had been placed for circular and longitudinal orientation. Zero degrees was defined as the site with the marker next to the arterial lumen (degree scale clockwise). Microphotography was performed for each section to ensure correct orientation. All sections were stained with hematoxylin-eosin and elastic Van Gieson's stains.

Analysis of ultrasound images: The ultrasound images were analyzed by 2 experienced investigators using stop-frame images; in cases of disagreement, analysis was repeated. Lumen diameter was defined as the arithmetic mean of the largest and smallest diameter. Luminal area was determined by planimetry after definition of the luminal border of intima. According to Tobis et al,[1,2] the media was defined as a circumferential, uniform echolucent zone. Tissue echoes, arising central to the media were defined as intima, those arising peripherally as adventitia. Thus, wall thickness was assessed by measuring the distance between the luminal border and the borderline between media and adventitia. Measurements of wall thickness were performed clockwise at 0°, 90°, 180° and 270°, with 0° representing the point nearest to the orientation marker. Atheromatous deposits were defined as either echolucent material within the intimal plaque (representing lipid deposits), hyperechogenic (representing fibromuscular/fibrous plaque) or hyperechogenic with dorsal shadowing (representing calcifications). Plaque thickness was determined radially as the maximal distance between the margins of the plaque. Measurements of luminal area and diameter were performed with and without echogenic contrast dye (SH U 508 = Laevovist), whereas all other measurements were based on the results after application of contrast dye. Perfusion pressure was maintained constant at 70 mm Hg during this procedure. The ringdown diameter was measured for both systems: 2.6 ± 0.07 mm for the rotating probe system and 2.0 ± 0.04 mm for the rotating mirror system (n = 20, p <0.0001). In vessels with a lumen smaller than the ringdown diameter (rotating transducer, n = 26; rotating mirror, n = 15), no reliable correlation could be found for either area or vessel wall measurements in both devices, whereas the correlation was equal or slightly improved in the remaining vessels. All measurements were performed online using software of the individual ultrasound device for analysis of linear dimensions and planimetry, and were repeated offline for determination of intraobserver variability using a Cardio-200 image analysis device (Kontron, Munich, Germany); for wall thickness measure-

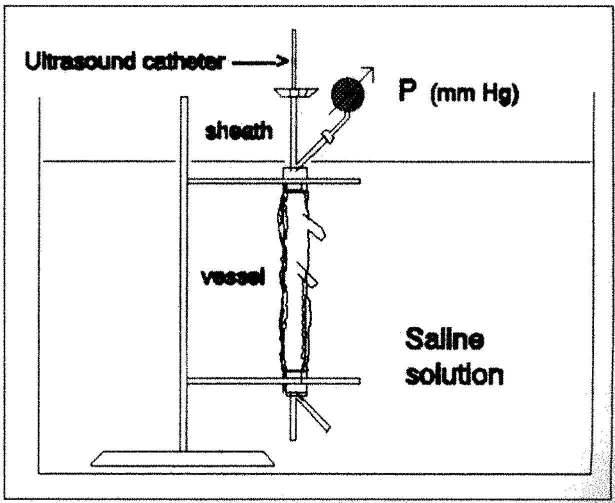

FIGURE 1. Experimental setting.

ments 64 sites were randomly selected. Intraobserver variability was 0.01 ± 0.73/0.04 ± 0.27 mm^2 for area, −0.06 ± 0.21/0.02 ± 0.26 mm for plaque, and −0.06 ± 26/−0.01 ± 0.14 mm for wall thickness measurements (rotating probe/mirror system); no observer bias was found. Definition of the vessel border by ultrasound along >270° of the circumference was possible in 62 of 64 segments by the rotating mirror system, but only in 44 by the rotating transducer system ($p < 0.001$) (Table I). Furthermore, there was a significant difference in the number of wall thickness measurements based on adequate imaging quality of the adventitial border: with use

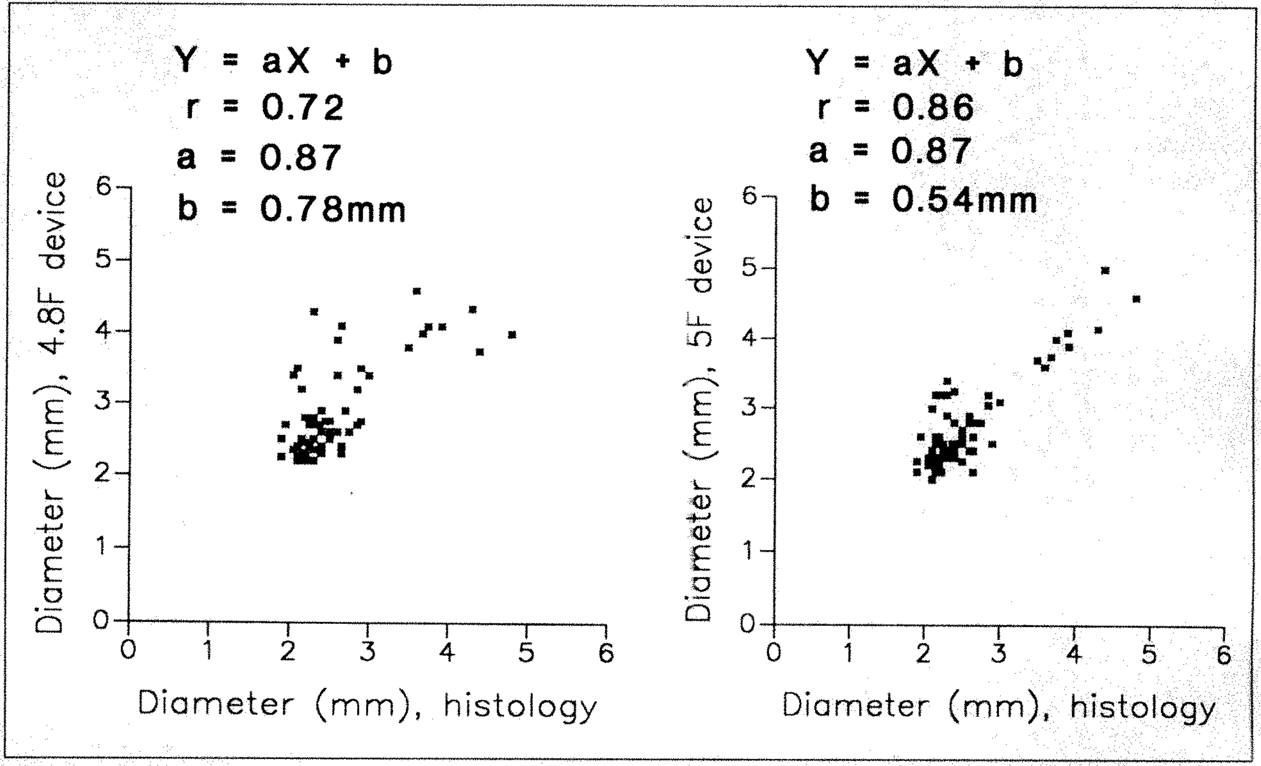

FIGURE 2. Plot of lumen diameter measurements by 2 different mechanical ultrasound devices compared with histologic measurements at the identical site; rotating probe system (4.8Fr) and rotating mirror system (5Fr device).

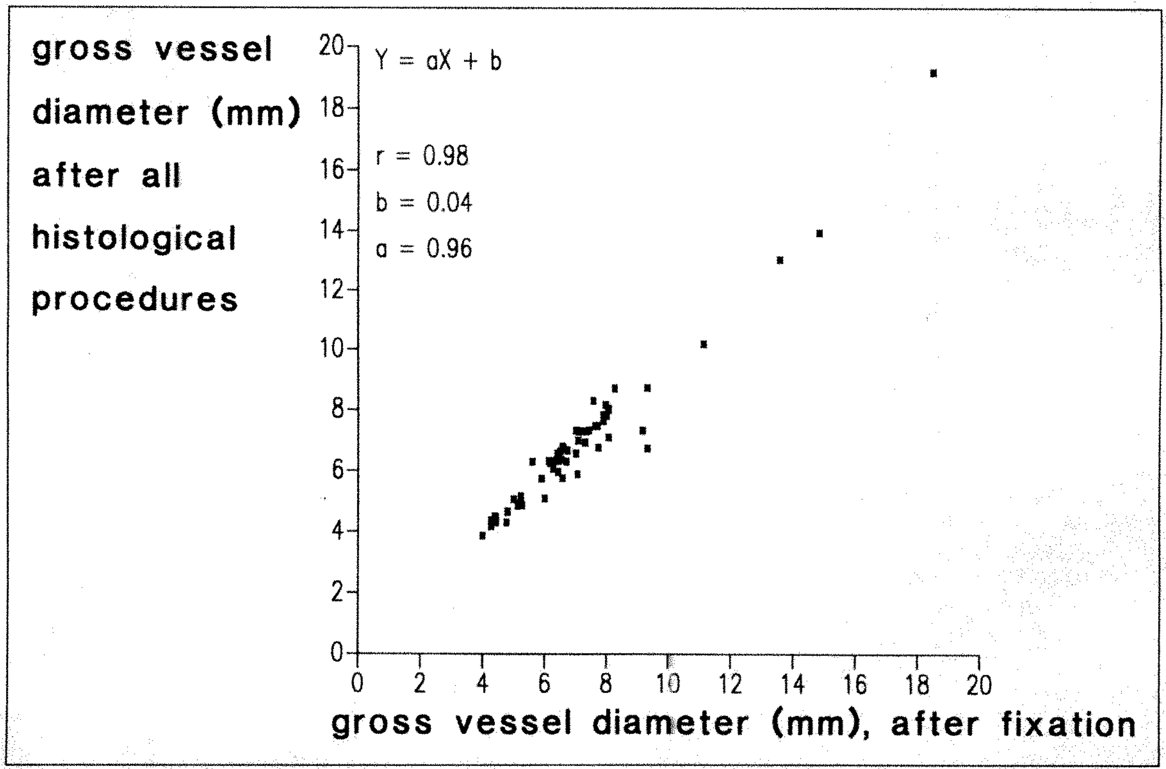

FIGURE 3. Plot of the gross vessel diameter of the perfusion-fixed coronary arteries before and after histologic procedures.

of the rotating mirror and rotating probe systems, 228 (89%) and 200 (78%) of 264 sites could be assessed ($p < 0.001$).

Analysis of histology: The histologic specimens were analyzed under light microscopy by a cardiovascular pathologist unaware of the ultrasound wall characterization and measurements. Morphometry was performed by a semiautomatic analysis device with previously validated software using a Reichert-Jung Mod. Univar microscope with tracing device and a modified digitizer (Summagraphics) with light point cursor (MTS GmbH, Tübingen, Germany) connected to a Commodore desktop computer. Qualitative and quantitative analyses were based on the same definitions used for the ultrasound imaging. Owing to artifacts from tissue processing, morphometry of vessel wall thickness was impossible at 4 of 256 sites of the 64 segments. Fifty-eight of the 64 images evaluated in this study had intimal thickening according to histologic criteria. In 51 of 64 segments (80%), distinct plaques were found by

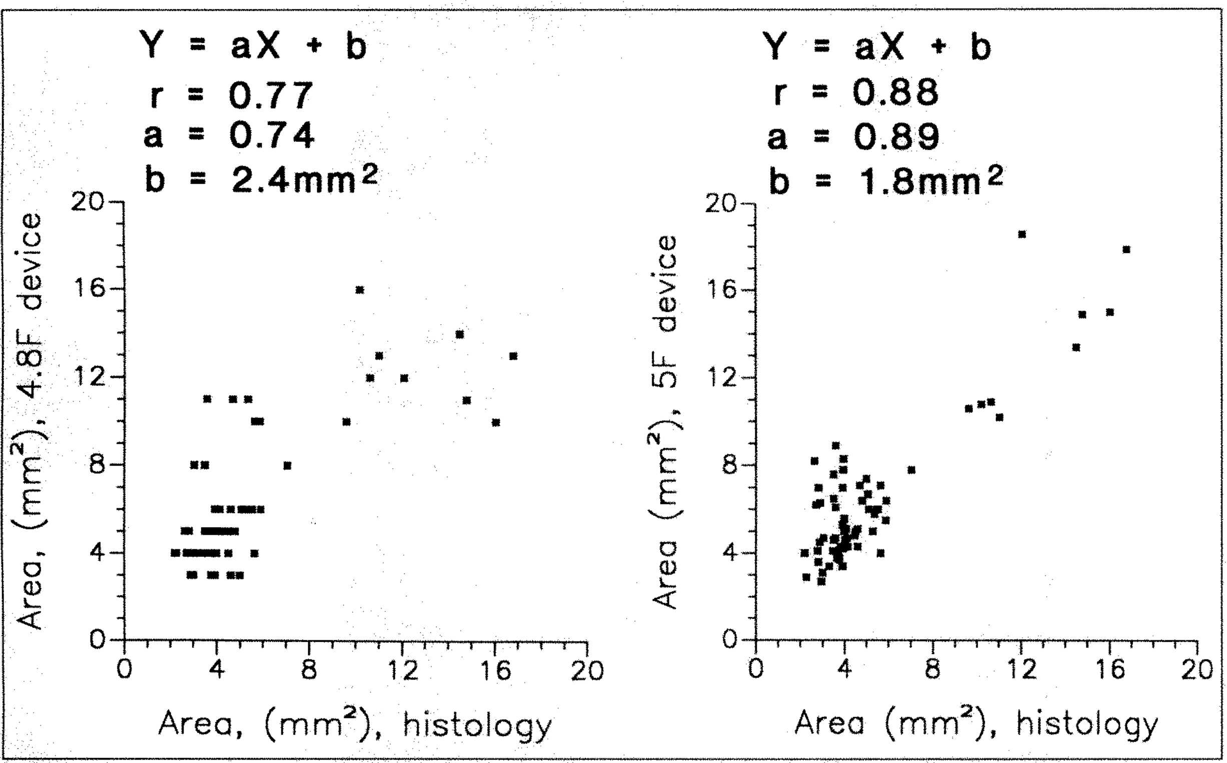

FIGURE 4. Plot of lumen area measurements by 2 different mechanical ultrasound devices compared with histologic measurements at the identical site; rotating probe system (4.8Fr) and rotating mirror system (5Fr device).

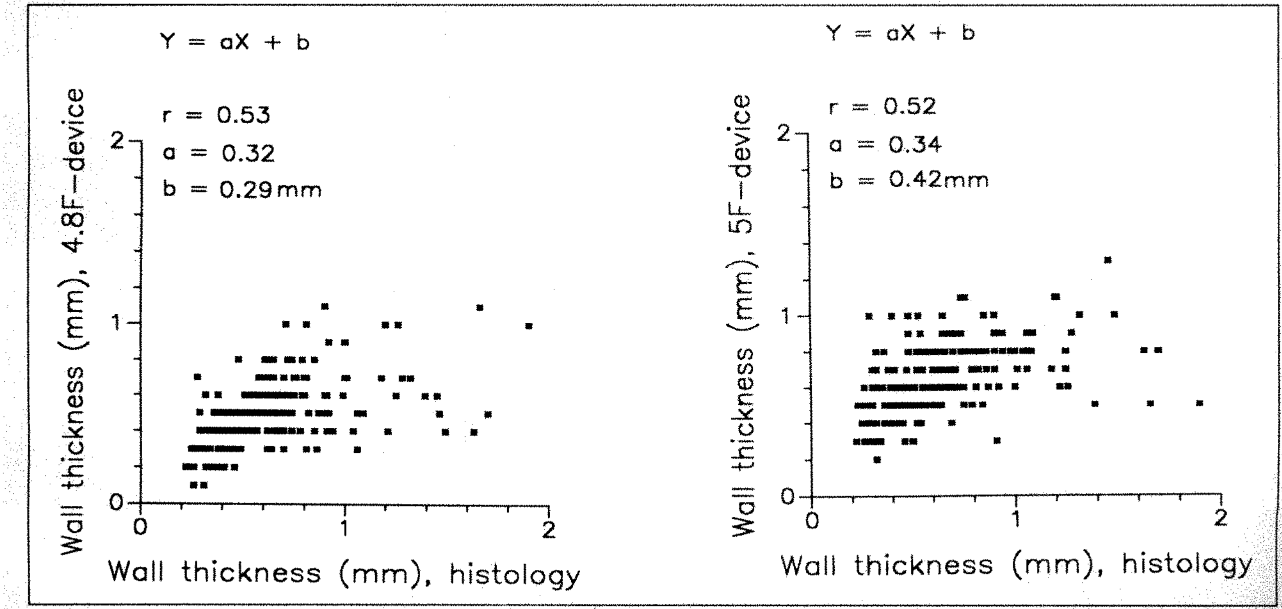

FIGURE 5. Plot of wall thickness measurements by 2 different mechanical ultrasound devices compared with histologic measurements at the identical site; rotating probe system (4.8Fr) and rotating mirror system (5Fr device).

histologic examination: They were located in the intima in 12 cases, and in the media in 7; in the remaining cases the lamina elastica interna as a borderline between intima and media was destroyed. Five plaques were calcified and 46 were found to be fibrous/fibromuscular. No intimal lipid deposits were found by histology.

Statistical analysis: Correlations between intravascular ultrasound and histology were determined by a linear regression analysis. The level of significance was tested with a probability value <0.05 as significant. Additionally, subgroups were formed according to the histologic lumen diameter (smaller vessels: lumen diameter ≤ 2.5 mm, $n = 26$; larger vessels: lumen diameter >2.5 mm, $n = 38$). Chi-square test and Student's paired *t* test were performed using a statistical program (PlotIT, TM) and Z values were calculated to compare different correlations. Intraobsever variability was determined for measurements of area, plaque and wall thickness.

RESULTS

Luminal diameter of the analyzed vessels was 2.6 ± 0.6 mm (mean ± SD, range 1.7 to 4.4) measured by histology, 2.8 ± 0.7 mm with the rotating mirror, and 2.9 ± 0.7 mm with the rotating transducer system. The correlation coefficient between ultrasound and histology was significantly better with the rotating mirror ($r = 0.86$) than with the rotating transducer system ($r = 0.72$, $p < 0.05$; Figure 2). Thus, diameter calculated from ultrasound was 17 ± 21 and 17 ± 22% higher than the morphometric values. According to the plot of the measurements of the perfusion-fixed arterial ring versus measurements of the corresponding histologic section (Figure 3), we were able to confirm the validity of our histologic findings.

Luminal area determined by histology was 5.3 ± 3.4 mm^2, by the rotating mirror system 6.5 ± 3.4 mm^2, and by the rotating transducer system 6.3 ± 3.2 mm^2. Correlation between intravascular ultrasound and histology was not statistically different for both systems ($r = 0.88$, rotating mirror system; $r = 0.77$, rotating probe system; Figure 4). Again, a slight overestimation of luminal area was found, which was significant ($p < 0.05$) only with the rotating mirror system (36 ± 49%; rotating probe 33 ± 46%), leading to an overestimation of area in 52 segments (81%), respectively. Subgroup analysis revealed that in vessels with a lumen diameter ≥ 2.5 mm, a good correlation between ultrasound and histology could be found for the rotating mirror system ($r = 0.88$, $y = 0.81x + 2.8$ mm^2; $p < 0.001$) and for the rotating probe system ($r = 0.76$, $y = 0.64x + 3.6$ mm^2; $p < 0.001$). In contrast, in smaller vessels (lumen diameter <2.5 mm), correlation between ultrasound and morphometry was reduced ($r = 0.48$, $p < 0.02$) using the rotating mirror system, whereas no relation was found with the rotating probe device.

Impact of contrast medium on intracoronary ultrasound: Luminal borders could be defined only after application of contrast dye in 3% using the rotating mirror and 22% using the rotating probe device ($p < 0.001$; see Table I). The number of area measurements that had to be corrected after application of contrast dye was significantly lower using the rotating mirror ($p < 0.001$;

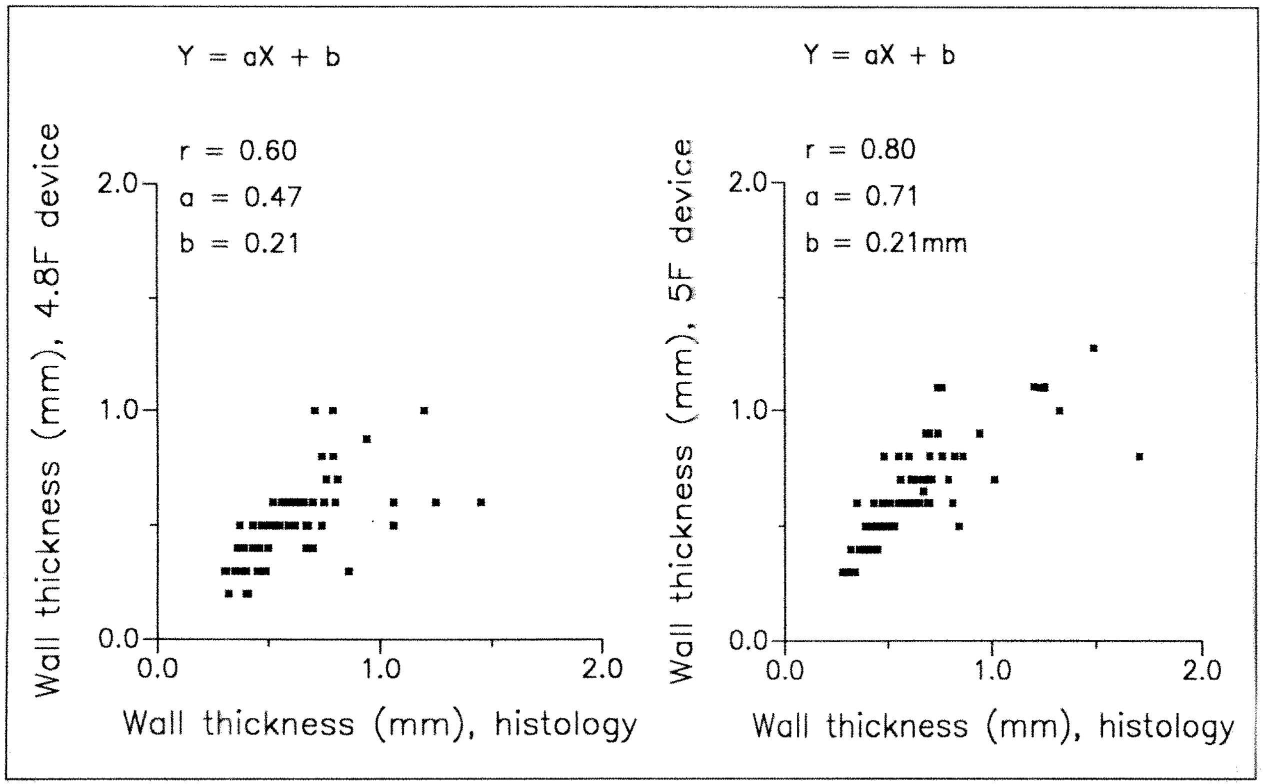

FIGURE 6. Subgroup analysis of large diameter vessels (diameter >2.5 mm): Plot of wall thickness measurements by 2 different mechanical ultrasound devices compared with histologic measurements at the identical site; rotating probe system (4.8Fr) and rotating mirror system (5Fr device)

TABLE II Analysis of Plaque Identification by Two Mechanical Ultrasound Devices Compared with Histologic Findings

	Correctly Identified Positive	False-Positive	False-Negative	Correctly Identified Negative
5Fr probe (rotating mirror)	82% 42 (of 51)	15% 2 (of 13)	18% 9 (of 51)	85% 11 (of 13)
4.5Fr probe (rotating probe)	63% 32 (of 51)	38% 5 (of 13)	37% 19 (of 51)	62% 8 (of 13)
	p <0.05	p = NS	p = NS	p = NS

TABLE III Plaque Identification in Small and Large Lumen Diameter Vessels: Number of Plaques That Were Not Recognized by Intracoronary Ultrasound in Different Vessel Sizes

Lumen Diameter	≤2.5 mm	>2.5 mm, <3 mm	≥3 mm	Total of False-Negative Plaques
Rotating mirror device	65% (n = 8)	18% (n = 1)	0% (n = 0)	n = 9
Rotating probe device	33% (n = 8)	33% (n = 8)	16% (n = 3)	n = 19

p = NS considering different lumen diameters.

Table I). Correlation coefficient for area measurements comparing ultrasound and histology could be elevated from 0.62 to 0.77 ($p < 0.04$) using the rotating probe system. With the rotating mirror system the use of contrast dye improved the correlation coefficient ($r = 0.82$ to $r = 0.88$; p = NS); measurements with this device had been possible in all cases in smaller vessels. A relation between ultrasound and histology was found ($r = 0.48$, $p < 0.02$) in this subgroup only with contrast dye and only with this device.

Vessel wall thickness determined by histology was 0.65 ± 0.33 and 0.64 ± 0.20 mm with the rotating mirror system and 0.49 ± 0.19 mm with the rotating transducer system. Correlation between ultrasound and histology was low ($r = 0.52$ and 0.53, respectively; Figure 5). The deviation between the rotating mirror system and histology was 12.4 ± 41.8% (rotating probe −12.5 ± 29.5%). A significantly ($p < 0.011$) more reliable relation was found in vessels >2.5 mm ($r = 0.80$) for the rotating mirror, but not for the rotating probe device ($r = 0.60$; Figure 6).

Plaque identification: With use of the rotating mirror system, 42 of 51 plaques were correctly identified (Table II) compared with 32 of 51 ($p < 0.05$) for the rotating probe device; all 5 calcified plaques were detected by either device. Characterization of plaque type was correct in all cases. Table III demonstrates the tendency toward false-negative results in small diameter vessels. In 2 (rotating mirror) and 5 (rotating probe device) sections, a sonolucent wall thickening was falsely described by ultrasound as plaque, which was not present on histologic examination (specificity not significantly different).

Plaque thickness was 1.06 ± 0.34 mm (histology), 0.98 ± 0.19 mm (rotating mirror device) and 1.06 ± 0.34 mm (rotating probe device). A relation between ultrasound and histology was found only for the rotating mirror system (Figure 7).

DISCUSSION

A comparison between mechanical ultrasound devices working with different technical principles has not been systematically performed in vitro in studies of coronary arteries. With the rotating mirror system, a good correlation between intravascular ultrasound and histol-

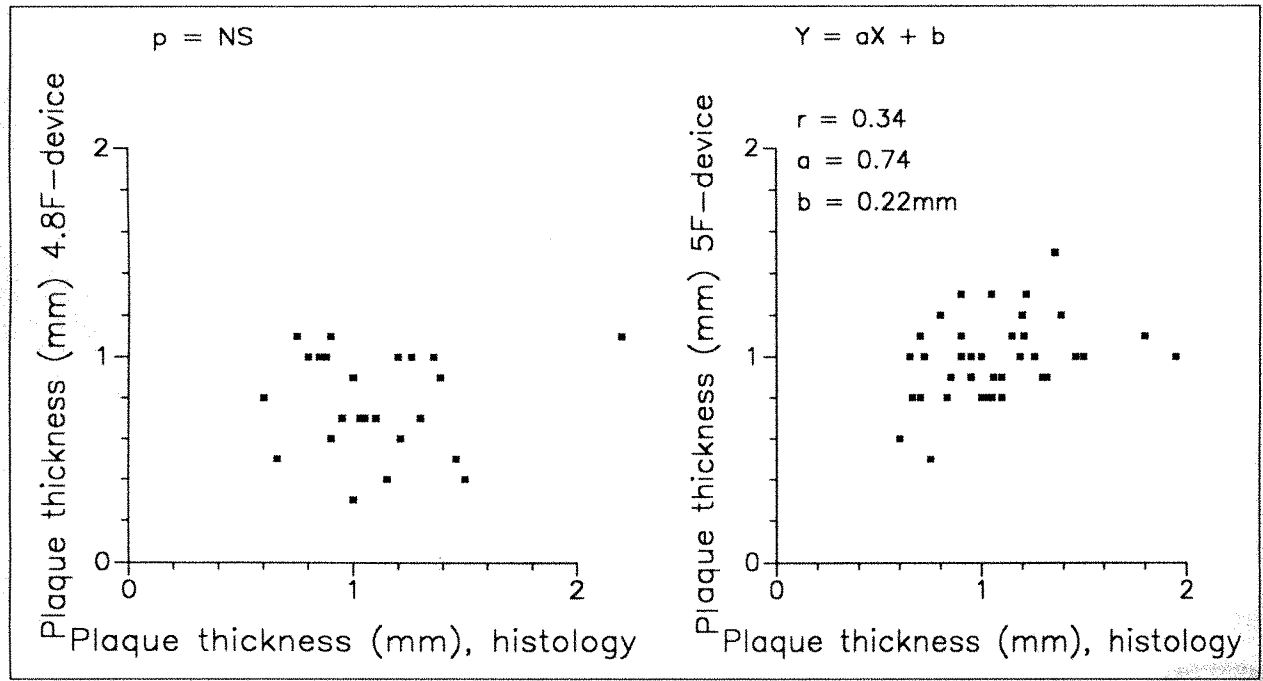

FIGURE 7. Plot of plaque thickness measurements by 2 different mechanical ultrasound devices compared with histologic measurements at the identical site; rotating probe system (4.8Fr) and rotating mirror system (5Fr device).

ogy for the quantification of lumen area was found (r = 0.88). These results are in agreement with the results reported by Potkin[4] and Tobis[1] and their co-workers who used an alternative 5Fr ultrasound system based on the same principle (r = 0.85 and 0.88, respectively). In contrast, for the rotating transducer system the correlation between ultrasound and histology was significantly lower in our study. The superiority of the rotating mirror system for determination of luminal dimensions in small coronary arteries underlines the better performance in the near field. This may be due to a smaller ringdown diameter (2 vs 2.6 mm), which is be achieved by an extention of the distance between transducer and the visualized object using a reflecting mirror. In contrast to several in vitro studies performed in peripheral arteries,[5,9] only a weak relation between ultrasound and histology was found for determination of wall thickness. However, none of the cited studies reported wall thickness measurements in vessels of such small dimensions. Subgroup analysis of the larger diameter vessels showed a relation between ultrasound and morphometry with the rotating mirror device comparable to the data of Gussenhoven[5] and Mallery[9] and their co-workers. We conclude that the results for vessel wall measurements in smaller vessels are due to the poor image quality of the ultrasound catheters in the near field. Furthermore, in all of the cited studies the vessel wall was isolated from the surrounding soft tissue (which facilitates determination of wall thickness), whereas in our study the surrounding soft tissue was preserved.

Plaque detection was possible in partially or totally calcified plaques, with a high accuracy by both systems, in agreement with the study of Potkin et al.[4] In contrast, recognition of fibrous plaques was limited especially with the rotating probe system. This may be due to the resolution capabilities, which currently cannot provide an accurate differentiation of isoechogenic structures. Again, the better performance of the rotating mirror device in the near field may contribute to the considerably better plaque detection with this system. False assumption or quantification of plaques can be explained by a tangential course of the ultrasound beam across the vessel wall, which can simulate isoechogenic wall thickening. The reason for the underestimation of wall and plaque thickness in the current study may be the dorsal shadowing of calcified or heavily fibrotic plaque, which limits the definition of the outer border of the vessel.[1–4,6,7,9,10]

No systematic studies on the impact of contrast medium for exact definition of luminal borders and, thus, visualization of luminal area have been reported. As demonstrated in this investigation, application of contrast medium allowed determination of lumen area in 3 and 16% of segments using the rotating mirror and rotating probe device, respectively, and improved quantitative measurements with both devices in 48 and 77% of all segments, respectively. Even in larger vessels an improvement of image quality could be achieved for both systems. Subgroup analysis, however, revealed that the effect of contrast dye was most pronounced in small diameter vessels. Furthermore, this better imaging quality in the near field may be very beneficial in assessing intraluminal structures.

Study limitations: We found a slight overestimation of vessel lumen by intravascular ultrasound, the effect of which may be due to shrinkage by tissue processing. Siegel et al[15] also reported a smaller lumen on histologic examination when comparing fresh tissue specimen before and after tissue processing (mean difference 26%). Furthermore, for different plaque types, varying shrinkage in plaques directly proportional to their water content was observed in various morphometric studies.[19–21] There was a significantly higher tendency toward overestimation of lumen area, especially in vessels with a small lumen, which may be explained by circular stretching by the catheter.

Conclusions: There are considerable differences in the accuracy of ultrasound measurements between mechanical systems. Nevertheless, additional application of contrast dye can improve accuracy of luminal measurements, especially in smaller vessels.

REFERENCES

1. Tobis JM, Mallery JA, Gessert J, Griffith J, Mahon D, Bessen M, Moriuchi M, McLeay L, McRae M, Henry WL. Intravascular ultrasound cross-sectional arterial imaging before and after balloon angioplasty in vitro. *Circulation* 1989; 80:873–882.

2. Tobis JM, Mallery JA, Mahon D, Lehmann K, Zalesky P, Griffith J, Gessert J, Moriuchi M, Mc Rae M, Dwyer ML, Greep N, Henry WL. Intravascular ultrasound imaging of human coronary arteries in vivo — analysis of tissue characterization with comparison to in vitro histological specimens. *Circulation* 1991;83:913–926.

3. Nishimura RA, Edwards WD, Warnes CA, Reeder GS, Holmes DR, Tajik AJ, Yock PG. Intravascular ultrasound imaging: in vitro validation and pathologic correlation. *J Am Coll Cardiol* 1990;16:145–154.

4. Potkin BN, Bartorelli AL, Gessert JM, Neville RF, Almagor Y, Roberts WC, Leon MB. Coronary artery imaging with intravascular high frequency ultrasound. *Circulation* 1990;81:1575–1585.

5. Gussenhoven EJ, Essed CE, Lancee CT, Mastik F, Frietman P, Van Egmond FCm, Reiber J, Bosch H, Van Hurk H, Roelandt J, Bom N. Arterial wall characteristics determined by intravascular imaging: an in vitro study. *J Am Coll Cardiol* 1989;14:947–942.

6. Nissen SE, Grines CL, Gurley JC, Sublett K, Haynie D, Diaz C, Booth DC, DeMaria AN. Application of a new phased-array ultrasound imaging catheter in the assessment of vascular dimensions: in vivo comparison to cineangiography. *Circulation* 1990;81:660–666.

7. Nissen SE, Gurley JC. Application of intravascular ultrasound for detection and quantification of coronary arteriosclerosis. *Int J Cardiac Imaging* 1991;6:165–177.

8. St. Goar F, Pinto FJ, Alderman EL, Fitzgerald PJ, Stadius ML, Popp RL. Intravascular ultrasound imaging of angiographically normal coronary arteries: An in vivo comparison with quantitative angiography. *J Am Coll Cardiol* 1991;18:952–958.

9. Mallery JA, Tobis JM, Griffith J, Gessert J, McRae M, Moussabeck O, Bessen M, Moriuchi M, Henry WL. Assessment of normal and arteriosclerotic arterial wall thickness with an intravascular ultrasound imaging catheter. *Am Heart J* 1990; 6:1392–1499.

10. Nissen SE, Gurley JC, Grines CL, Booth DC, McClure R, Berk M, Fischer C, DeMaria AN. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. *Circulation* 1991;84:1087–1099.

11. Borst C, Savalle LH, Smits PC, Post MJ, Gussenhoven WJ, Bom N. Imaging of post-mortem coronary arteries by 30 MHz intravascular ultrasound. *Int J Cardiac Imaging* 1991;6:239–246.

12. Isner JM, Rosenfield K, Losordo DW, Rose L, Langevin RE, Razvi S, Kosovsky BD. Combination balloon-ultrasound imaging for percutaneous transluminal angioplasty. Validation of imaging, analysis of recoil and identification of plaque fracture. *Circulation* 1991;84:739–754.

13. Neville JR, Yasuhara H, Watanabe BI, Canady J, Durán W, Hobson RW. Endovascular management of arterial intimal defects: an experimental comparison by arteriography, angioscopy and intravascular ultrasonography. *J Vasc Surg* 1991;13:496–502.

14. Yock PG, Fitzgerald PJ, Sudhir K, Linker DT, White W, Ports A. Intravascular ultrasound imaging for guidance of atherectomy and other plaque removal techniques. *Int J Cardiac Imaging* 1991;6:179–189.

15. Siegel RJ, Ariani M, Fishbein MC, Chae JS, Park JC, Maurer G, Forrester JS. Histopathologic validation of angioscopy and intravascular ultrasound. *Circulation* 1991;84:109–117.

16. Gussenhoven WJ, Essed CE, Frietmann P, Mastik F, Lancée C, Slager C, Serruys P, Gerritsen P, Pietermann H, Bom N. Intravascular echocardiographic assessment of vessel wall characteristics: correlation with histology. *Int J Cardiac Imaging* 1989;4:105–116.

17. Rosenfield K, Losordo DW, Ramaswami K, Pastore JO, Langevin RE, Razvi S, Kosowsky BD, Isner JM. Three-dimensional reconstruction of human coronary and peripheral erteries from images recorded during two-dimensional intravascular ultrasound examination. *Circulation* 1991;84:1938–1956.

18. Waller BF. Anatomy, histology and pathology of the major epicardial coronary arteries relevant to echocardiographic techniques. *J Am Soc Echo* 1989;2: 232–252.

19. Siegel RJ, Swan K, Edwalds G, Fishbein MC. Limitations of postmortem assessment of human coronary artery size and luminal narrowing: differential effects of tissue fixation and processing on vessels with different degrees of arteriosclerosis. *J Am Coll Cardiol* 1985;5:342–346.

20. Stowell RE. Effect on tissue volume of various methods of fixation, dehydration and embedding. *Stain Tech* 1941;16:67–83.

21. Baker JR. The reactions of fixatives with tissue cells. Methods of research. In: Principles of Biological Microtechnique. London: Methuen, 1958:76–88.

Left Atrial Appendage Flow Velocity Assessment Using Transesophageal Echocardiography in Nonrheumatic Atrial Fibrillation and Systemic Embolism

Patrick M. J. Verhorst, MD, Otto Kamp, MD, Cees A. Visser, MD,
and Freek W. A. Verheugt, MD

Fifty-four patients with nonrheumatic atrial fibrillation (AF) were studied: 16 patients with (group I) and 38 patients without (group II) documented systemic embolism. Transesophageal echocardiography (TEE) was performed to evaluate the presence of left atrial (LA) appendage thrombus and LA spontaneous contrast, LA size, systolic and diastolic peak velocity of the left pulmonary vein, and forward and backward peak velocity of the LA appendage. No difference was observed in the presence of LA thrombus between the 2 groups. The occurrence of LA spontaneous contrast was significantly ($p = 0.01$) higher in the group with embolism. LA size, measured by atrial length (4.96 ± 0.84 vs 4.79 ± 1.38 cm; $p =$ NS) and atrial width (4.50 ± 0.96 vs 4.31 ± 1.24 cm; $p =$ NS), was the same for both groups and thus not associated with embolism. There was no difference in systolic peak velocity (0.39 ± 0.22 vs 0.44 ± 0.22 m/s; $p =$ NS), and a trend toward a higher diastolic peak velocity (0.50 ± 0.17 vs 0.42 ± 0.15 m/s; $p = 0.08$) was seen in the left pulmonary vein in the group with embolism. Forward (0.25 ± 0.19 vs 0.39 ± 0.23 m/s; $p < 0.05$) and backward (0.23 ± 0.15 vs 0.33 ± 0.16 m/s; $p < 0.05$) peak velocities of the LA appendage were significantly lower in the embolism group. Assessment of LA appendage flow velocity may potentially identify patients with nonrheumatic AF at high risk for systemic embolism.

(Am J Cardiol 1993;71:192–196)

Systemic embolism is a well-known potential complication in patients with atrial fibrillation (AF).[1–5] Emboli may occur from thrombi forming within the left atrium and left atrial (LA) appendage.[1,4,6] Transesophageal echocardiography (TEE) has proven to be a superior technique in imaging the left atrium and LA appendage.[7,8] We performed TEE to identify patients with nonrheumatic AF at (higher) risk of systemic embolism.

METHODS

Study patients: From February 1 to December 1, 1990, 54 patients with nonrheumatic AF were studied; they were classified into 2 groups: Group I consisted of 16 patients admitted because of a suspected systemic embolism, 14 patients with stroke and 2 patients with peripheral embolism documented by computer tomography scan or angiography, or both. Group II, the control group, consisted of 38 patients without previous systemic embolism, who were first seen in our heart emergency room with complaints of palpitations or chest discomfort, or both. All patients had electrocardiographically documented AF on admission. Patients with a mitral stenosis or a prosthetic heart valve were excluded.

Transesophageal echocardiographic study: TEE was performed within 48 hours after admission with a Hewlett-Packard ultrasonograph (HP 77020 AC) with a 5 MHz phased-array single-plane transesophageal transducer. Parameters evaluated by TEE were the presence of LA appendage thrombus, LA spontaneous contrast, LA size (length and width), and systolic and diastolic peak velocity of the left pulmonary vein, and forward and backward peak velocity of the LA appendage. The LA cavity and LA appendage were adequately visualized by TEE, and 2 independent observers evaluated the presence of LA appendage thrombus or LA spontaneous contrast, or both. LA size was measured and analyzed in the 4-chamber view in end-systole.[7] Velocities of pulmonary venous flow[9] and LA appendage flow were obtained using pulsed Doppler with the lowest possible filter setting (5 or 10 cm/s). They were registered in the direction of the flow within an angle of 30° with the transducer; optimal alignment was thus assessed using simultaneous color flow imaging. Pulmonary venous flow velocity measurements were obtained with the sample volume placed in the left upper pulmonary vein ≥ 5

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mm from the origin of the pulmonary vein into the left atrium (Figure 1). The sample volume was placed in the LA appendage, just below the basis of the appendage, to obtain LA appendage flow velocity measurements (Figure 1). Measurements of the left pulmonary venous flow velocity and LA appendage flow velocity were recorded on a strip chart recorder at 50 and 100 mm/s, respectively. Mean values of the peak systolic and diastolic velocities of the left pulmonary vein flow, and peak forward and backward velocities of LA appendage flow were obtained in 3 consecutive cardiac cycles in patients with sinus rhythm and in 10 cardiac cycles in patients with AF at the time of TEE.

Statistics: Statistical analysis was performed by using the Student's *t* test (p values) for continuous variables and the chi-square test to compare groups on the basis of categorical variables. Results are expressed as mean ± SD.

RESULTS

Patient characteristics: The baseline clinical characteristics including age, gender, duration and etiology of AF were similar in both groups (Table I).

TABLE I Patient Characteristics and Outcome of Transesophageal Echocardiography

	Group I With Embolism (n = 16)	Group II Without Embolism (n = 38)	p Value
Demographics			
Mean age (year)	69	61	NS
Men/women	8/8	24/14	NS
CAD	7	9	NS
Systemic hypertension	6	6	NS
Valvular heart disease	6	12	NS
Hyperthyroidism	0	3	NS
Other diseases	3	8	NS
Lone AF	3	16	NS
Duration of AF (mos)	25	21	NS
Paroxysmal AF	12	26	NS
Prior aspirin	1	0	NS
Prior anticoagulant	3	4	NS
Variables			
LA thrombus	1 (6%)	0	NS
LA spontaneous contrast	6 (38%)	2 (5%)	0.01
LA length (cm)	4.96 ± 0.84	4.79 ± 1.38	NS
LA width (cm)	4.50 ± 0.96	4.31 ± 1.24	NS
Systolic peak velocity pulmonary vein (m/s)	0.39 ± 0.22	0.44 ± 0.22	NS
Diastolic peak velocity pulmonary vein (m/s)	0.50 ± 0.17	0.42 ± 0.15	0.08
Forward peak velocity LA appendage (m/s)	0.25 ± 0.19	0.39 ± 0.23	<0.05
Backward peak velocity LA appendage (m/s)	0.23 ± 0.15	0.33 ± 0.16	<0.05

AF = atrial fibrillation; CAD = coronary artery disease; LA = left atrial.

Transesophageal echocardiography: At the time of TEE examination, 31 patients had AF and 23 had sinus rhythm. The outcome of TEE is presented in Table I. We observed no difference in the presence of LA thrombus between the 2 groups. The occurrence of LA spontaneous contrast was significantly (p = 0.01) higher in the group with than without embolism. LA size was the same for both groups and thus not associated with embolism. There was no difference in systolic peak velocity, and we found a trend (p = 0.08) for a higher diastolic peak velocity of the left pulmonary vein in the group with embolism. LA appendage peak flow velocities were significantly (p <0.05) associated with systemic embolism in patients with nonrheumatic AF. When categorizing patients by cardiac rhythm during TEE in patients with AF and sinus rhythm, only a trend for lower appendage peak flow velocities was observed in the embolism group (Figure 2).

DISCUSSION

AF is a common disease; its prevalence increases with age.[1,2,3,6] It is associated with a high risk of systemic embolism (annual incidence 5.5%).[1,2,10] Apart from the often dramatic morbidity and mortality, systemic embolism has a great impact on our society. With a growing elderly population the incidence of systemic embolism will increase correspondingly, making it a matter of urgent concern in the near future.

Before the results of recent studies, there was the dilemma of antithrombotic treatment, weighing the reduced risk embolism against the increased risk of bleeding. There is enough evidence that patients with AF benefit from antithrombotic treatment, which significantly reduces the risk of embolism with only a few bleeding complications.[11–14] Thus far, warfarin appears preferable to aspirin despite the low but still persistent risk of bleeding.

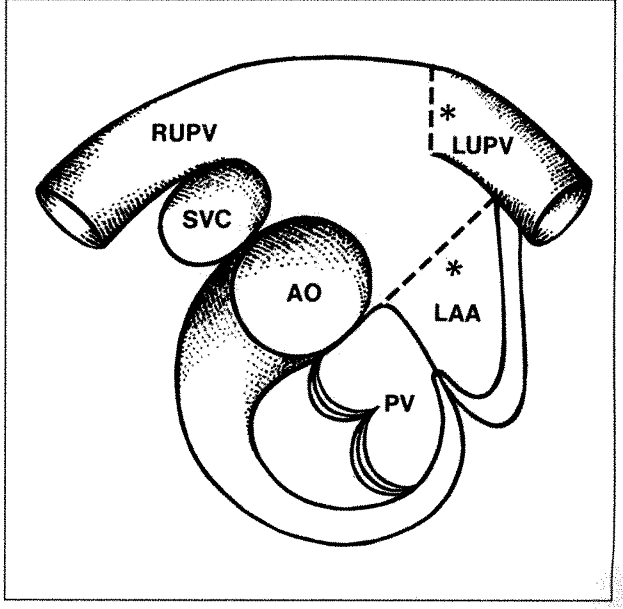


FIGURE 1. Transverse view. Ao = aorta; LAA = left atrial appendage (*sample volume); LUPV = left upper pulmonary vein (*sample volume); PV = pulmonary valve; RUPV = right upper pulmonary vein; SVC = superior vena cava.

An objective and measurable laboratory test is needed to predict a low or high risk of embolism in patients with AF. Echocardiography, and especially the transesophageal approach, may provide such a test.

Naturally, the presence of LA appendage thrombus increases the likelihood of a cardiac origin. In one study of 11 patients with nonrheumatic AF and an embolus, 4 patients (36%) had LA thrombus.[15] We observed only 1 patient (6%) with LA thrombus.

LA spontaneous contrast is experimentally and clinically related to low flow rates.[8] A recent study demonstrated that LA spontaneous contrast is an independent predictor of thromboembolic risk in patients with nonvalvular AF.[16] In this study, we found significantly more cases of LA spontaneous contrast in patients with embolism.

LA enlargement is associated with AF by the fact that AF probably contributes to LA enlargement rather than being caused by it.[6,17] Previous studies regarding the predictive value of LA enlargement for embolism have not been conclusive.[10,18] However, a recent large, prospective study showed that LA size was significant-

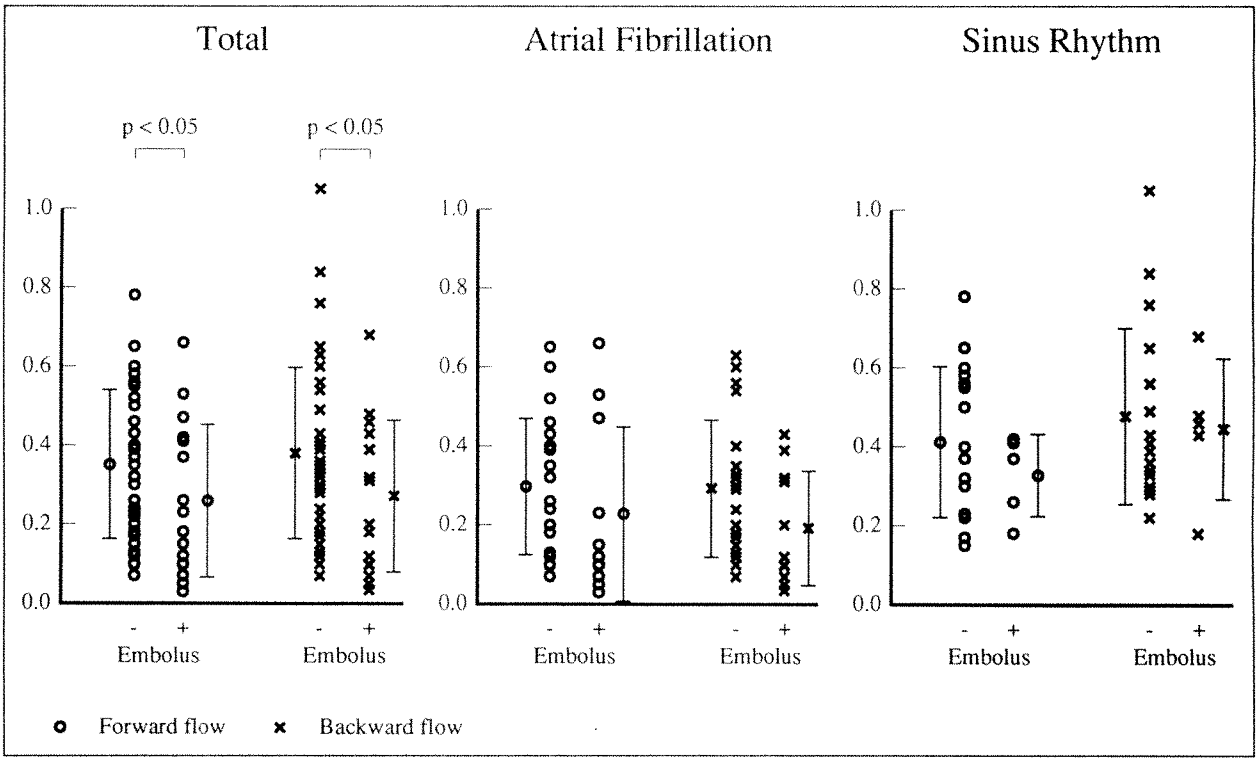


FIGURE 2. Left atrial appendage flow velocity (m/s) related to absence (–) or presence (+) of systemic embolus.

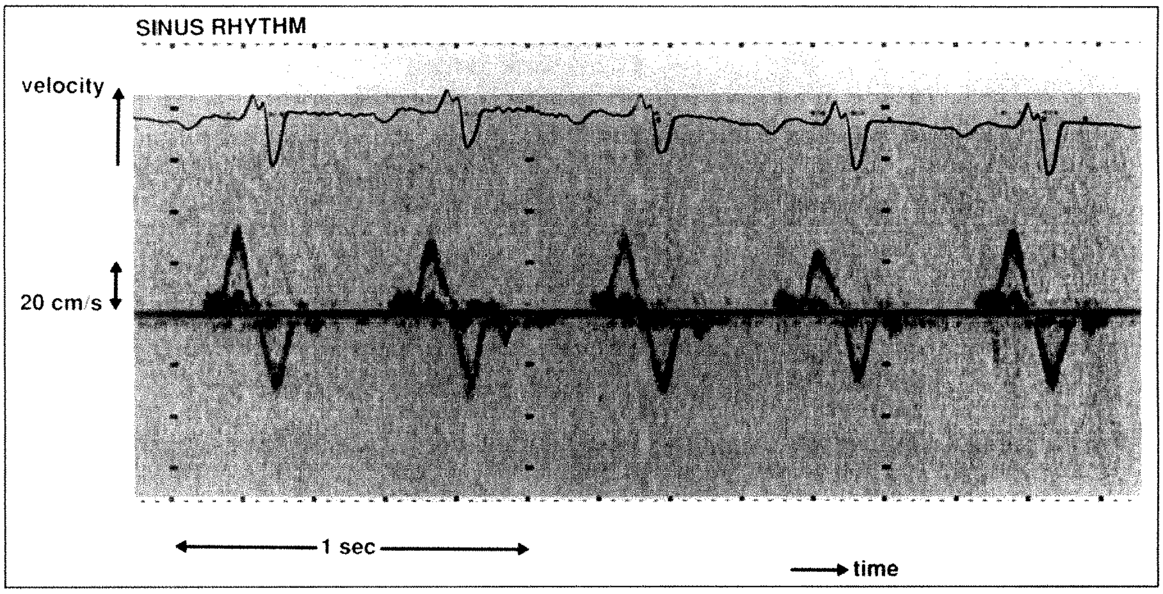


FIGURE 3. Doppler echocardiogram of left atrial appendage in a patient with sinus rhythm. Biphasic flow corresponds with contraction and relaxation of the left atrial appendage after the P wave.

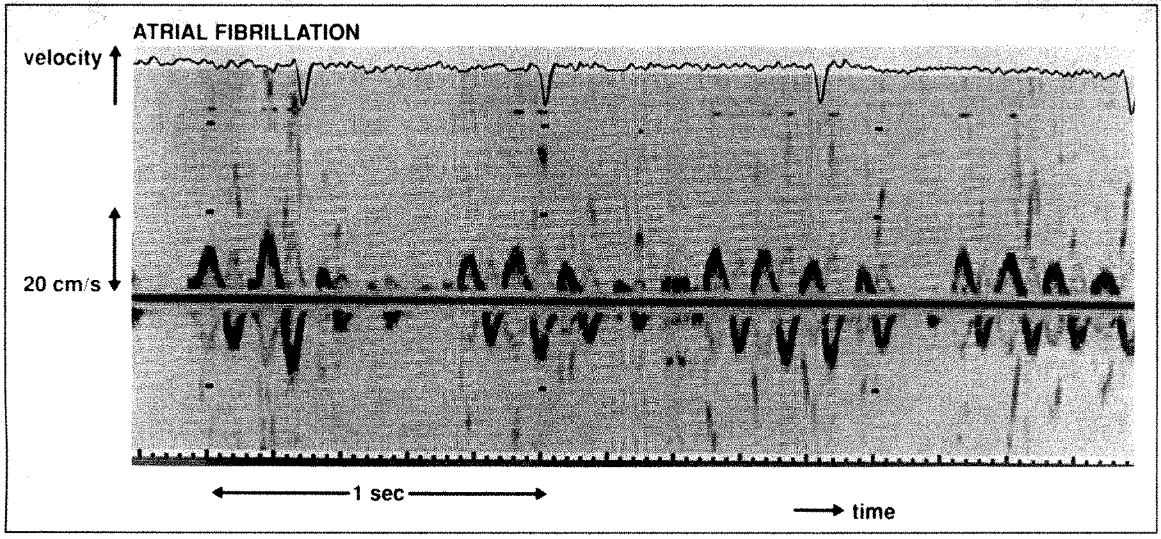


FIGURE 4. Doppler echocardiogram of left atrial appendage in a patient with atrial fibrillation. The flow signal displays a sawtooth appearance, and the peak flow velocity is reduced compared with velocity during sinus rhythm.

ly related to the incidence of embolism.[19] In our small study we could not demonstrate a significant difference.

Pulmonary venous flow velocity is a reflection of the pressure gradient between the pulmonary veins and the left atrium. Atrial relaxation is one of the factors responsible for systolic forward flow. Diastolic forward flow reflects the transmitral filling pattern. In the absence of atrial contraction, as in AF, forward flow is still present, although of lower velocity than diastolic forward flow.[9] Velocity measurement of pulmonary venous flow, especially systolic peak velocity, might be able to predict mean pressure.[20] In the group with embolism, there was only a tendency for a higher diastolic peak velocity.

Examination of the outlet of the LA appendage provided information about emptying (forward peak velocity) and filling (backward peak velocity) of the LA appendage. In sinus rhythm, a biphasic flow pattern representing LA appendage contraction and relaxation followed the P wave on the electrocardiogram (Figure 3). In AF, a sawtooth appearance was seen throughout the cardiac cycle with lower forward and backward velocities (Figure 4). A small study demonstrated the value of assessing thrombogenesis in the LA appendage by analysis of blood flow velocities in the LA appendage. Peak flow velocity was significantly less in patients with nonrheumatic AF and a cerebral infarction, compared with patients with no cerebral infarction ($p < 0.05$).[21] We confirmed these results in our study, finding significantly lower forward and backward peak flow velocities in the LA appendage in patients with nonrheumatic AF and systemic embolism, compared with patients without embolism. A recent study found that LA appendage thrombus formation is associated with LA appendage contraction and dilatation.[22]

Study limitations: A problem with studying systemic embolism of cardiac origin is that the diagnosis itself is notoriously difficult. This might explain the rather large standard deviation due to the inclusion of patients without embolism of cardiac origin.

With regard to LA spontaneous contrast, we are aware that its value is limited by the fact that its day-to-day occurrence is not known, and that the accuracy of the diagnosis is influenced by transducer gain-setting and interobserver variability.[16]

Another limitation is the fact that the study group was too small to perform multivariant analysis in order to observe independent predictive parameters and to find a cutoff point in LA appendage flow velocity to distinguish between patients with and without embolism. Studies with a larger group size will probably provide that information.

Clinical implications: AF is a common disease associated with high risk of embolism, which can be significantly reduced by antithrombotic treatment, especially warfarin. Identifying how embolism occurs and knowing what precipitates it has important implications for its treatment and prevention. Such identification would make it possible to define subgroups of patients at high or low risk, needing more or less aggressive therapy.

LA spontaneous contrast, and more particularly the objective and measurable LA appendage peak flow velocity may be used to identify patients with AF prone to systemic embolism. Using these parameters, one can define high- and low-risk groups to be randomized for treatment with warfarin versus aspirin. This requires further study in large prospective trials.

REFERENCES

1. Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. *Stroke* 1985;16:182–188.

2. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. *JAMA* 1985;254:3449–3453.

3. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke* 1986;17:622–626.

4. Sherman DG. Cardiac embolism: the neurologist's perspective. *Am J Cardiol* 1990;65:32C–37C.

5. Petersen P. Thromboembolic complications of atrial fibrillation and their prevention: a review. *Am J Cardiol* 1990;65:24C–28C.

6. Come PC, Riley MF, Bivas NK. Roles of echocardiography and arrhythmia monitoring in the evaluation of patients with suspected systemic embolism. *Ann*

Neurol 1983;527–531.

7. Drexler M, Erbel R, Muller U, Wittlich N, Mohr-Kahaly S, Meyer J. Measurements of intracardiac dimensions and structures in normal young adult subjects by transesophageal echocardiography. *Am J Cardiol* 1990;65:1491–1496.

8. Pearson AC, Labovitz AJ, Tatineni S, Gomez C. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. *J Am Coll Cardiol* 1991;17:66–72.

9. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography. *Circulation* 1990;81:1488–1497.

10. Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation. Risk of stroke and role of antithrombotic therapy. *Circulation* 1991;84:469–481.

11. Roy D, Marchand E, Gagne B, Chabot M, Cartier R. Usefulness of anticoagulant therapy in the prevention of embolic complications of atrial fibrillation. *Am Heart J* 1986;112:1039–1043.

12. Petersen P, Boysen G, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK Study. *Lancet* 1989; 1:175–179.

13. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation study: final results. *Circulation* 1991;84:527–539.

14. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C for the CAFA Study Coinvestigators. Canadian Atrial Fibrillation Anticoagulant (CAFA) Study. *J Am Coll Cardiol* 1991;18:349–355.

15. Malone SA, Palac RT, Imus RL, Andrilenas KK, McDonald RW, Giraud GD. Prevalence of left atrial thrombi in symptomatic versus asymptomatic patients with nonvalvular atrial fibrillation (abstr). *Circulation* 1989;80 (suppl II):II–1.

16. Black IW, Hopkins AP, Lee LCL, Walsh WF, Jacobson BM. Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. *J Am Coll Cardiol* 1991;18:398–404.

17. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation* 1976;53:273–279.

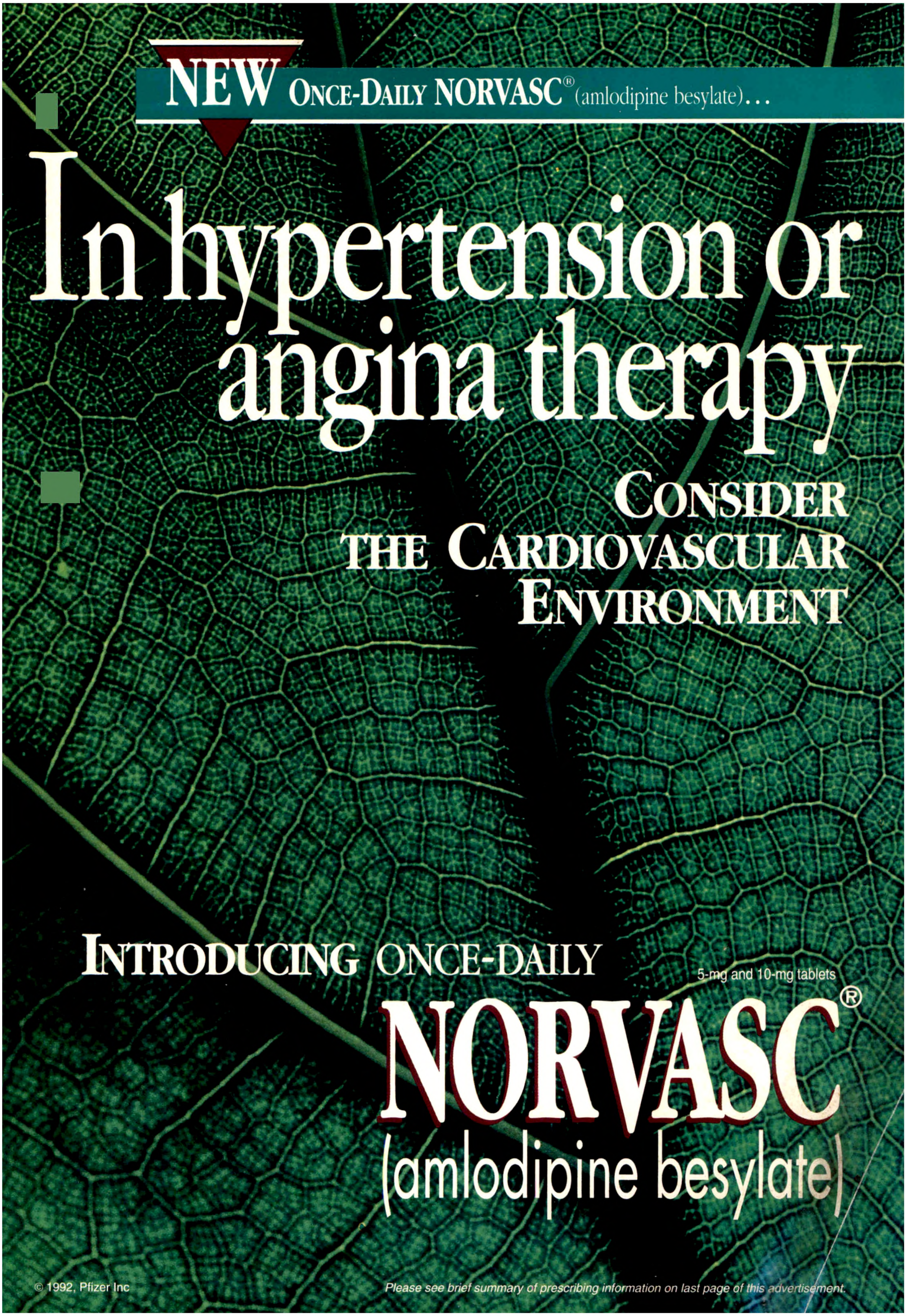
18. Cabin HS, Clubbs KS, Hall C, Perlmutter RA, Feinstein AR. Risk for systemic embolization of atrial fibrillation without mitral stenosis. *Am J Cardiol* 1990; 65:1112–1116.

19. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;116:6–12.

20. Kuecherer HF, Muhiudeen IA, Kusumoto FM, Lee E, Moulinier LE, Cahalan MK, Schiller NB. Estimation of mean left atrial pressure from transesophageal pulsed Doppler echocardiography of pulmonary venous flow. *Circulation* 1990;82: 1127–1139.

21. Suetsugu M, Matsuzaki M, Toma Y, Anno Y, Maeda T, Okada K, Konishi M, Ono S, Tanaka N, Hiro J, Nishimura Y, Kusukawa R. Detection of mural thrombi and analysis of blood flow velocities in the left atrial appendage using transesophageal two-dimensional echocardiography and pulsed Doppler flowmetry. *J Cardiol* 1988;18:385–394.

22. Pollick CP, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. *Circulation* 1991;84:223–231.



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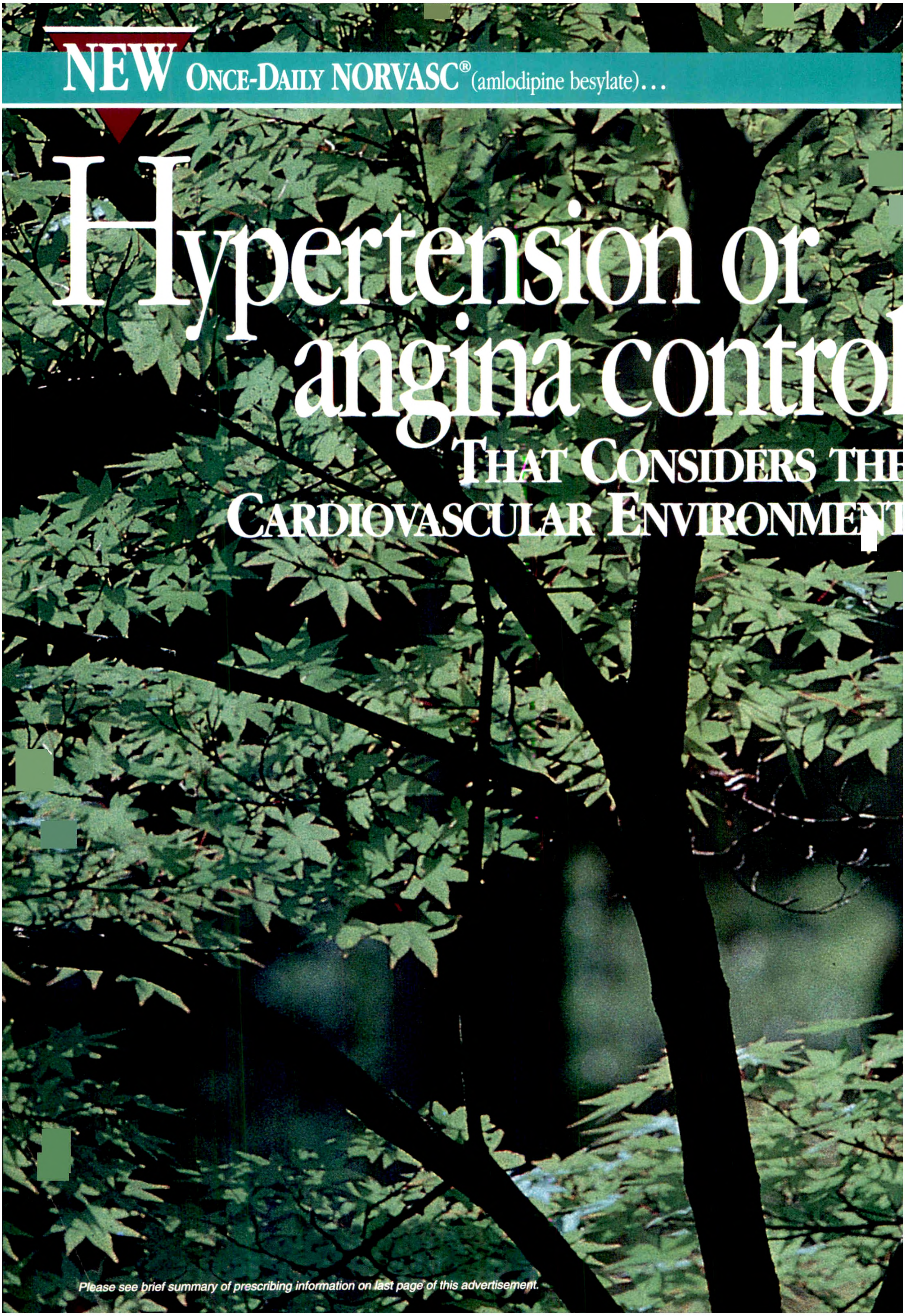
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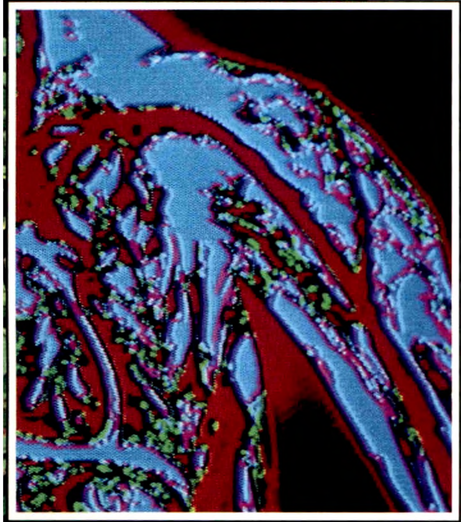
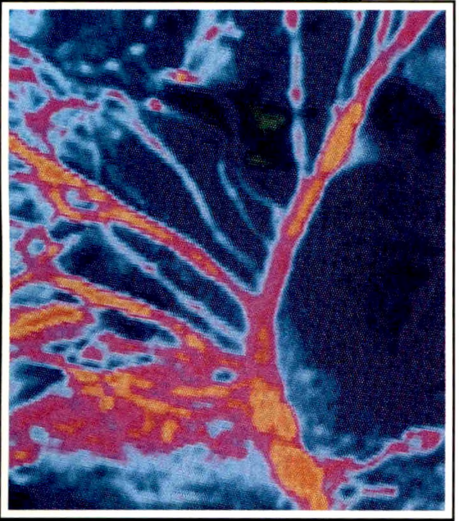


Arteriogram of peripheral vasculature



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Coronary angiogram of a normal heart

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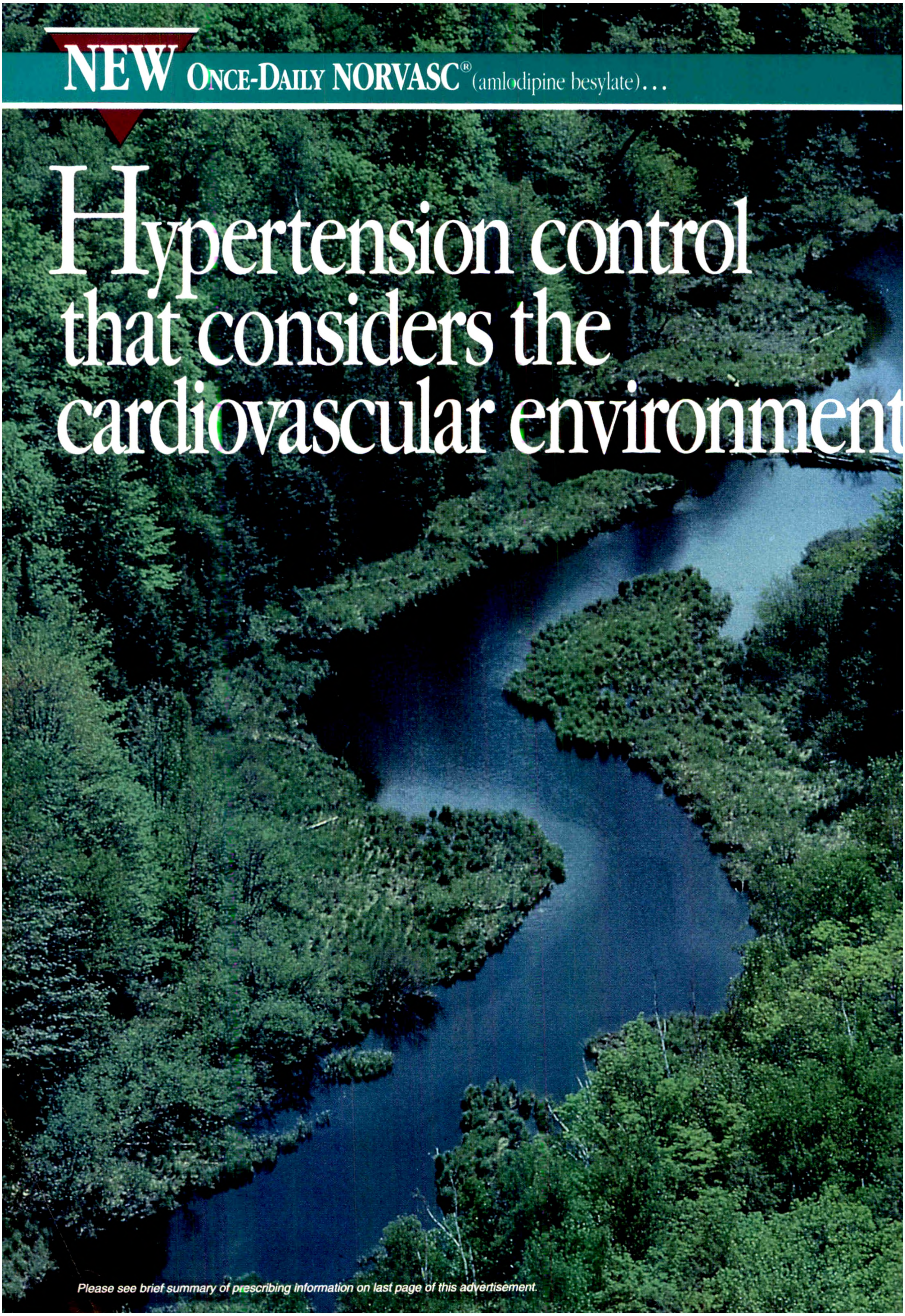
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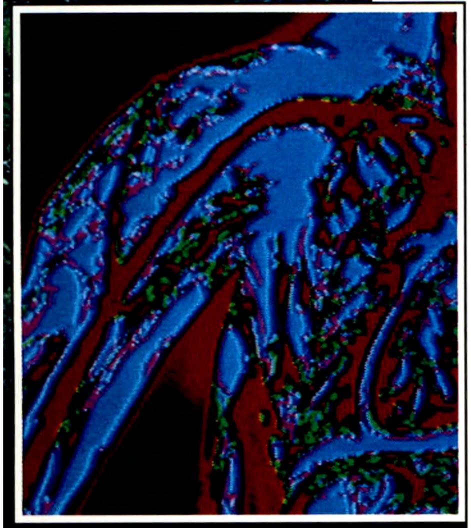
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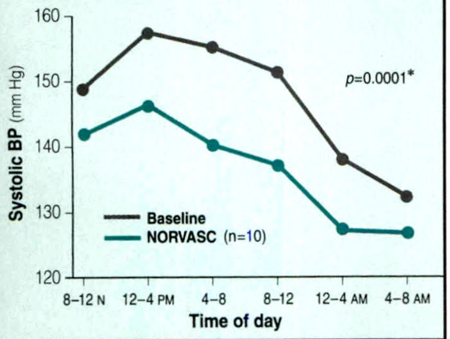
Mean systolic blood pressure (BP) over 24 hours (week 4 data)[1]



Results of a double-blind, randomized, parallel, placebo-controlled study of NORVASC on ambulatory BP in 15 evaluable hypertensive patients (diastolic BP range: 95 to 114 mm Hg): 10 on NORVASC, 5 on placebo. A 4-week, single-blind, placebo run-in period was followed by 4 weeks of double-blind therapy. Ambulatory BP was measured for 24 hours at the end of the placebo run-in phase and after double-blind therapy. (Data on file.[1])

*Average of mean BP values over 24 hours at week 4 versus baseline averages.

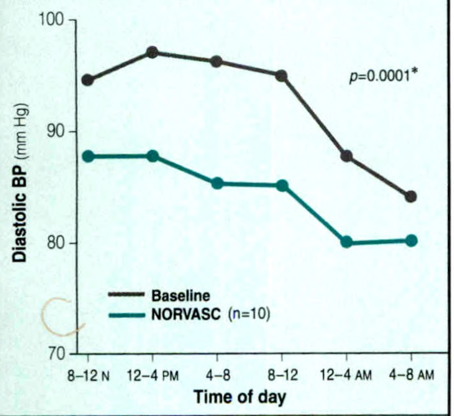
SAFETY

Excellent tolerability

- 92% of patients remained on NORVASC for 1 year in a long-term study[2]
- No clinically significant effects on heart rate[1] or cardiac conduction[1]; no negative inotropic effects at clinical doses in hemodynamic studies,† even when administered with beta blockers to humans[1]
- No adverse effect on lipid levels[1]
- No adjustment in the starting dose is required for patients with renal dysfunction, even those on hemodialysis[3]

† Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.

Mean diastolic BP over 24 hours (week 4 data)[1]



(Data on file.[1])

*Average of mean BP values over 24 hours at week 4 versus baseline averages.

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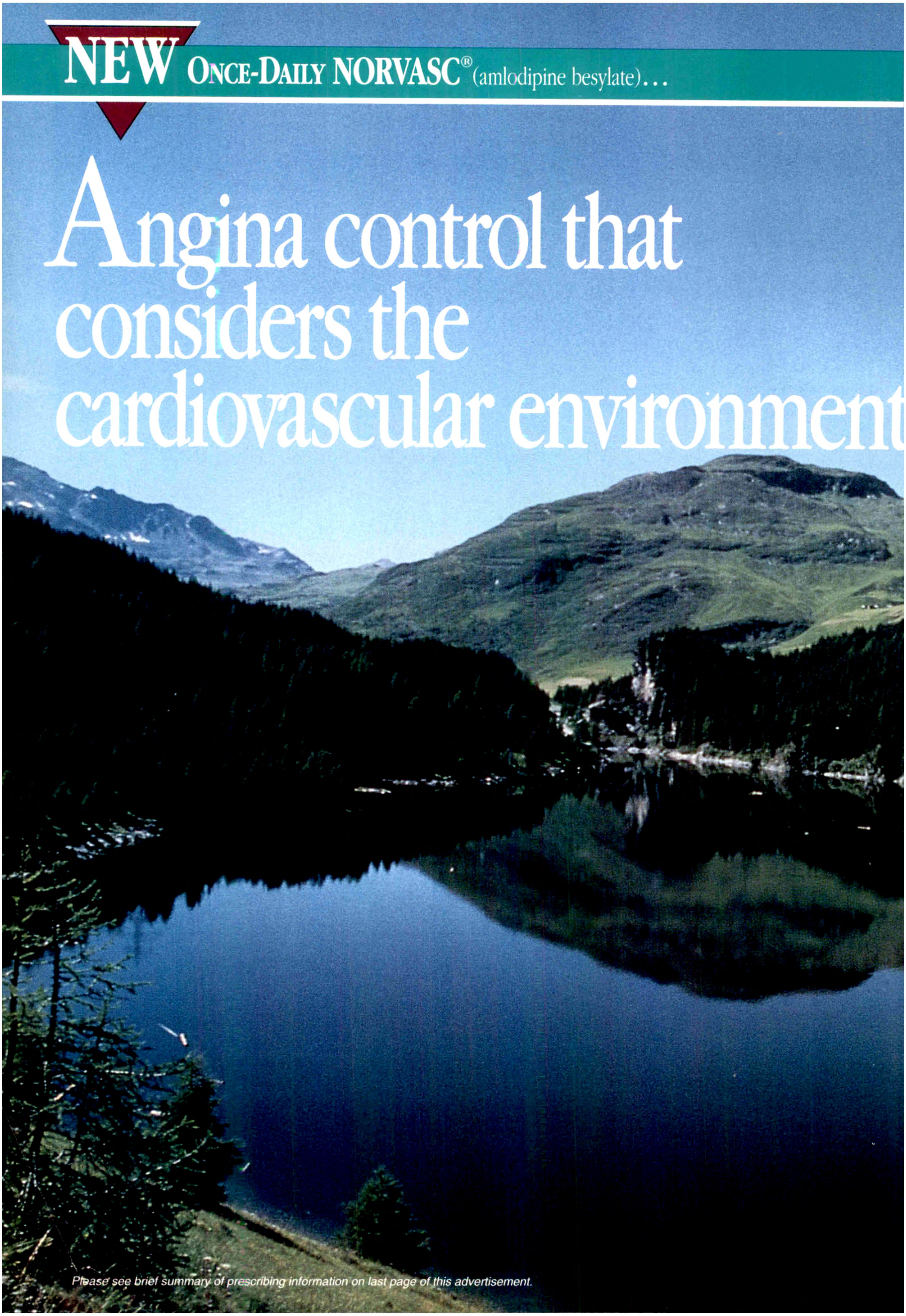
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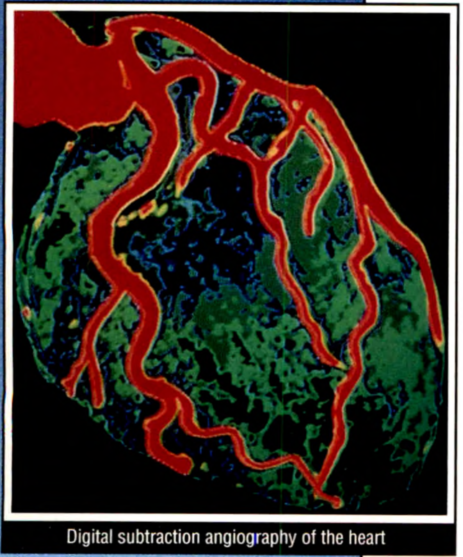
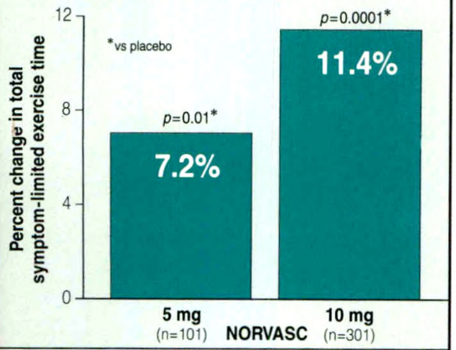
- No clinically significant effect on heart rate[1] or cardiac conduction[1]
- No negative inotropic effects at clinical doses in hemodynamic studies,[‡] even when administered with beta blockers to humans[1]
- No drug interaction with digoxin, warfarin, or cimetidine[1]

[‡] Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.



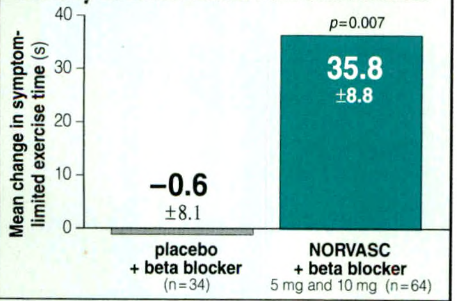
Digital subtraction angiography of the heart

Change in symptom-limited exercise time measured 24 hours postdose[1]



Data from eight placebo-controlled, double-blind, randomized studies of the effect of NORVASC on symptom-limited exercise time. All studies included a 2-week, single-blind, placebo run-in period. The eight studies included five monotherapy trials and three add-on therapy trials. Treatment ranged from 4 to 6 weeks. Placebo group (n=297) had a 2.1% increase in symptom-limited exercise time. Exercise time at baseline: placebo, 480 sec; 5 mg, 523 sec; 10 mg, 493 sec. (Data on file.[1])

Efficacy in combination with beta blockers[†,1]



Results of a double-blind, placebo-controlled, parallel-dose response, multicenter trial in 134 stable exertional angina patients. Patients received beta-blocker therapy for at least 4 weeks prior to entry. After a 2-week, single-blind, placebo run-in period with uninterrupted beta-blocker treatment, patients were randomized to receive NORVASC (2.5, 5, or 10 mg qd) or placebo for a 4-week treatment period. Data are presented for combined NORVASC groups (5 and 10 mg only) (n=67 patients entered) and placebo (n=34). Baseline values (NORVASC vs placebo)—symptom-limited exercise time (seconds): 518 (n=64) vs 498; angina onset: 400 (n=61) vs 368; time to 1-mm ST-segment depression: 457 (n=29) vs 440 (n=15). (Data on file.[1])

[†] Caution should be used in patients with heart failure who are receiving known cardiodepressants such as beta blockers in combination with NORVASC.

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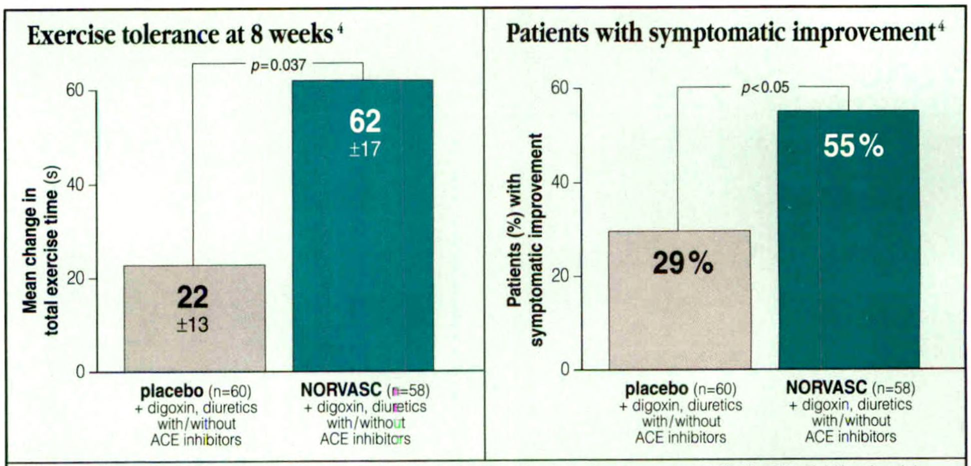
Dose-related side effects

Adverse event	NORVASC (%) 5 mg (n=296)	NORVASC (%) 10 mg (n=268)	placebo (%) (n=520)
Edema	3.0	10.8	0.6
Dizziness	3.4	3.4	1.5
Flushing	1.4	2.6	0.0
Palpitation	1.4	4.5	0.6

Caution should be exercised when using CCBs in any patient with heart failure

— In a double-blind study of 118 patients with mild to moderate CHF, NORVASC did not adversely affect cardiac function in patients with impaired LV function (LV ejection fraction <40%)[4]



Results of a randomized, multicenter, double-blind, placebo-controlled trial of NORVASC in 118 patients with well-compensated CHF. All had New York Heart Association (NYHA) Class II or III symptoms, with LV ejection fractions <40% (averaging 25%[1]). NORVASC dose: 10 mg qd. Patients were already on therapy with digoxin and diuretics, and 80 patients were also taking angiotensin-converting enzyme (ACE) inhibitors. (Adapted from Packer M et al, *J Am Coll Cardiol*, 1991.[4]) CHF patients did not have active angina or hypertension at the time of the study. Baseline exercise values: NORVASC, 570 sec; placebo, 613 sec. Symptomatology rating based on investigators' subjective global assessment. (Data on file.[1])

— In this study, NORVASC did not increase plasma norepinephrine levels and ejection fraction did not change[4]

— Studies in patients with NYHA Class IV heart failure have not been performed

— NORVASC therapy, despite these findings, should be used with caution in patients with heart failure until safety in these patients can be confirmed with additional clinical experience

Please see brief summary of prescribing information on last page of this advertisement.

DOSING

Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension
  - —In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily
- Titration can proceed to 10 mg
  - —Most angina patients will require 10 mg
- Can be taken with or without food

℞
Norvasc
5 mg
Sig: 1 tab
#30

NEW, ONCE-DAILY NORVASC®

5-mg and 10-mg tablets

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **3.** Doyle GD, Donohue J, Carmody M, Laher M, Greb H, Volz M. Pharmacokinetics of amlodipine in renal impairment. *Eur J Clin Pharmacol.* 1989;36:205-208. **4.** Packer M, Nicod P, Khandheria BR, et al. Randomized, multicenter, double-blind, placebo-controlled evaluation of amlodipine in patients with mild-to-moderate heart failure. *J Am Coll Cardiol.* 1991;17:274A. Abstract.

Brief Summary
NORVASC® (amlodipine besylate) Tablets
For Oral Use

CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in NYHA Class II-III heart failure patients have shown that NORVASC did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of the beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t ½) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N = 1730) in doses up to 10 mg to placebo (N = 1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension; **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting; **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** thirst; **hemopoietic:** purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

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* Based on patient weight of 50 kg.

** These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

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Comparison of Biphasic and Monophasic Shocks for Defibrillation Using a Nonthoracotomy System

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L. Brent Mitchell, MD, Henry J. Duff, MD, Robert S. Sheldon, MD, PhD, Teresa M. Kieser, MD,
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A comparison of defibrillation thresholds was made using biphasic and monophasic shocks delivered by a nonthoracotomy lead system in 2 clinically distinct groups of patients. The first group were patients receiving an implantable cardioverter-defibrillator who were studied before surgery with their chests closed. The second group were patients undergoing coronary artery bypass grafting (CABG) who were studied before surgery with their chests open but reapproximated. Biphasic defibrillation thresholds (stored energy) were significantly ($p < 0.001$) less than monophasic ones in subjects with the implantable cardioverter-defibrillator (12.3 ± 5.3 vs 21.1 ± 9.3 J) or CABG (14.6 ± 7.1 vs 24.2 ± 12.6 J). These values are less than were previously reported with a similar nonthoracotomy lead configuration. There were no significant differences between the 2 groups in all measurements derived from corresponding shock waveforms, although impedance tended to be greater in patients with CABG. However, subjects with CABG had greater left ventricular ejection fractions and did not have history of potentially lethal ventricular arrhythmias. Despite these differences, the conclusion that biphasic shocks are more effective would have been made in a study of either group alone. It is concluded that patients with CABG who have not had preceding potentially lethal ventricular arrhythmias may be a potential source of surrogate subjects for defibrillation research such as epicardial mapping, which requires that the chest be open.

(Am J Cardiol 1993;71:197–202)

The traditional source of human subjects for defibrillation research is patients who are receiving an implantable cardioverter-defibrillator (ICD) after having a prior episode of potentially lethal ventricular tachyarrhythmia. The increasing use of nonthoracotomy lead systems limits research instrumentation that requires an open chest (i.e., epicardial mapping). Surrogate subjects for the latter type of defibrillation research may be useful. Patients undergoing electrosurgery for Wolff-Parkinson-White syndrome have been used as subjects for defibrillation research.[1,2] The use of this patient population has been questioned,[3] and the use of surgery in such patients has diminished with the increased use of radiofrequency catheter ablation. Patients undergoing coronary artery bypass grafting (CABG) may be considered as surrogate subjects for defibrillation research. CABG is common, and 1 clinical trial is implanting ICDs in high-risk patients undergoing CABG who have not had a ventricular tachyarrhythmia.[4] However, the comparability of results of defibrillation research performed in such patients and that performed in ICD candidates with spontaneous ventricular tachyarrhythmias has not been established. Accordingly, as part of an evaluation of the efficacy of transvenous monophasic and biphasic defibrillation shocks in humans, we also compared the results in closed-chest ICD patients and open-chest CABG patients.

METHODS

Patient selection: Patients undergoing ICD implantation without concomitant surgery constituted the first group, and those undergoing CABG without concomitant surgery constituted the second group. The latter patients were excluded from the study if they had left main coronary artery disease or unstable angina in the month before surgery. With the specific approval of each patient's cardiologist, cardiac surgeon and anesthetist, all patients gave written, informed consent. This study and its consent form were approved by the local institutional review board. The cardiac surgeon and anesthetist had the option of withdrawing the patient from the study intraoperatively if they were concerned regarding the patient's clinical status.

Defibrillation threshold determination: All patients were studied under general anesthesia, which generally included a short acting narcotic (fentanyl or sufentanil), a sedative (midazolam), a neuromuscular blocking agent (vecuronium, pancuronium or metocurine) and a volatile anesthetic (enflurane, halothane or isoflurane). There

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From the Divisions of Cardiology and Cardiovascular Surgery, University of Calgary/Foothills Hospital, Calgary, Alberta, Canada, and Medtronic Inc., Minneapolis, Minnesota. This study was supported by the Heart and Stroke Foundation of Alberta, Calgary, Alberta, Canada, and by Medtronic Inc., Minneapolis, Minnesota, and was presented in abstract form at the Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Toronto, Ontario, Canada. Manuscript received April 30, 1992; revised manuscript received and accepted August 17, 1992.

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TABLE I Experimental Subjects

No.	Age (yr) & Sex	Weight (kg)	LVEF	Clinical Diagnosis	Presenting Rhythm	Medications	DFT (J)	
							Monophasic	Biphasic
CABG, Open-Chest Group								
1	56M	88.5	—	CAD	—	Diltiazem	37.8	22.6
2	68M	97.0	0.72	CAD	—	Diltiazem	37.7	22.8
3	65M	117.5	0.48	CAD	—	Diltiazem	13.7	6.9
4	54M	85.0	—	CAD, MI	—	—	42.4	23.4
5	57M	89.6	0.75	CAD	—	—	21.3	14.1
6	69M	84.3	0.69	CAD, MI	—	Nifedipine	28.1	16.9
7	70F	54.8	0.48	CAD, MI	—	Diltiazem	14.1	8.8
8	69F	50.6	0.72	CAD	—	Nifedipine	11.5	5.7
9	72M	69.2	0.72	CAD, MI	—	Propranolol	11.2	10.4†
Mean	64 ± 7	81.8 ± 20.9	0.65 ± 0.12				24.2 ± 12.6	14.6 ± 7.1†
ICD, Closed-Chest Group								
1	45F	59.0	0.55	HCM	VF	Verapamil	12.4	7.9
2	78M	76.0	0.18	CAD, MI	VT	Amiodarone	10.1	5.1
3	68M	72.0	0.20	CAD, MI	VF	—	26.9	13.4
4	60M	68.0	0.32	CAD, MI	VT	—	23.2	18.3
5	56M	67.0	0.22	CAD, MI	VT	—	18.6	11.1
6	73M	72.0	0.34	CAD, MI	VT	—	10.5	2.6
7	69M	72.0	0.26	CAD, MI	VT	—	37.7	15.8
8	47M	73.4	0.29	CAD, MI	VT	Propranolol	22.5	14.2
9	58M	65.0	0.30	IDCM	VT	—	8.4	8.8
10	18F	63.3	0.72	ARVD	VT	—	26.5	16.4
11	53M	83.5	0.51	IDCM	—	—	26.9	13.7
12	66M	67.5	0.24	CAD, MI	VT	—	30.4	19.8
Mean	58 ± 16	69.9 ± 6.4	0.34 ± 0.17*				21.2 ± 9.3	12.3 ± 5.3†

*$p < 0.05$; †$p < 0.001$, monophasic versus biphasic.

ARVD = arrhythmogenic right ventricular dysplasia; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DFT = defibrillation threshold, stored energy; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; IDCM = ideopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

were no differences in anesthetic use between the 2 groups of patients. A Medtronic model 10284 transvenous defibrillation catheter (electrode surface area 4.26 cm^2) was positioned with its tip at the right ventricular apex through a femoral vein. This electrode was the cathode for the first pulse. A small R2 defibrillator skin patch (Critical Care Products Division, Darox Corporation; electrode surface area 50.24 cm^2) was positioned high (top edge, level with manubrial angle) in the left axilla (center at midaxillary line) and was the anode for the first pulse. All shocks were delivered from a Medtronic model 2394 defibrillator. Patients were randomly assigned to receive either a monophasic or biphasic shock during the first episode of ventricular fibrillation. A crossover design assessed the alternate waveform during the second episode of ventricular fibrillation. Patients were fibrillated using alternating current delivered through the endocardial electrode catheter, and shocks were administered 10 seconds after cessation of alternating current fibrillation.

For both monophasic and biphasic shocks, the leading-edge voltage of the initial shock was 580 V (approximately 20 J). The nominal tilt of all pulses was 65% (approximate pulse duration 5 ms). The biphasic shock was supplied from a single capacitor and thus the leading-edge voltage of the second pulse was equal to the

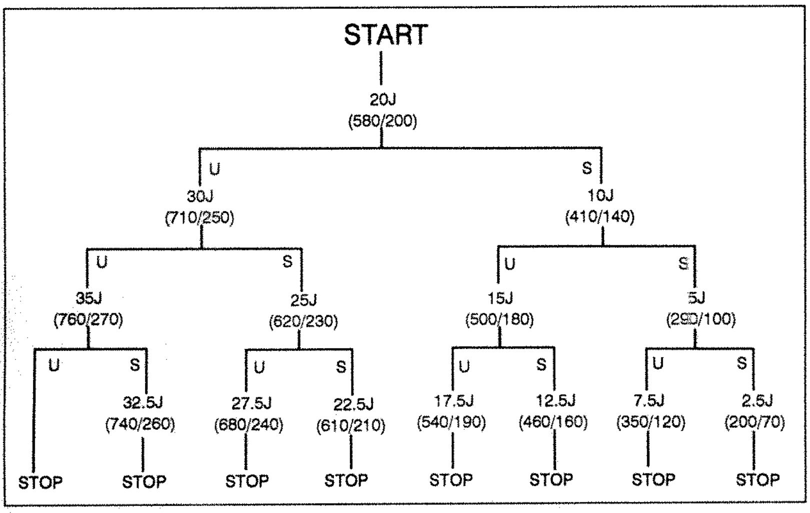

FIGURE 1. Schema for measurement of defibrillation thresholds. *Numbers in parentheses* are voltages of leading edge of pulses 1 (monophasic and biphasic) and 2 (biphasic), respectively. S = successful; U = unsuccessful.

terminal voltage of the first pulse. The polarity of pulse 2 was the reverse of pulse 1. The nominal tilt of the second pulse remained 65%, and the 2 pulses (approximately 5 ms each) were separated by 0.2 ms. The sequence of shocks used to determine defibrillation threshold used a binary search method (Figure 1). Defibrillation threshold was defined as the lowest energy providing successful defibrillation (Figure 1). Both stored and delivered energies were calculated.

Patients undergoing ICD implantation were tested with the chest closed before any surgery. Patients undergoing CABG were studied after median sternotomy and venous cannulation without cardiopulmonary bypass, but with the sternum reapproximated.

Data acquisition and analysis: The defibrillator was connected to a Honeywell VR 16 oscillographic recorder and a Hewlett-Packard tape recorder by a Medtronic model 2394004 breakout module. These recorders were used to simultaneously obtain surface electrocardiographic leads I, aVF and V_1, an intracardiac electrogram from the electrode catheter, and a marker channel from the ICD. The voltage and current delivered to the patient were recorded and measured on a Nicloet 3091 oscilloscope connected through Medtronic model 2707 signal isolation units. One channel of the oscilloscope was used to record voltage and another to measure current. The voltage and current of the leading and trailing edges of each pulse were measured and from these values, tilt, impedance and stored and delivered energy were calculated.

Continuous data are presented as mean ± 1 SD. Comparisons were obtained by paired or unpaired *t* test, as appropriate. Proportional data were compared using Fisher's exact test. Statistical significance was accepted at $p < 0.05$. Curve-fitting used linear regression. All calculations were performed using commercially available, computer programs (MRTOD, Seattle, Washington).

RESULTS

Patients: The clinical characteristics of the 2 groups of patients are presented in Table I. Four of 9 patients with CABG had a previous myocardial infarction. Eight of 12 patients in the ICD group had coronary artery disease, and all 12 had a previous myocardial infarction. The remaining 4 patients in the latter group had cardiomyopathy (2 idiopathic dilated, and 1 each hypertrophic and right ventricular arrhythmogenic).

A major difference between the 2 groups was that no patient with CABG had had lethal ventricular arrhythmias compared with all but 1 ICD patient. The patient with arrhythmogenic right ventricular dysplasia was an 18-year-old with a strong family history of sudden death and inducible, sustained ventricular tachycardia. The mean left ventricular ejection fraction was significantly less for ICD patients.

Approximately 90% of ICD patients approached consented to participate, and 3 were excluded intraoperatively because ventricular fibrillation could not be induced through the endocardial catheter. Approximately 25% of patients with CABG approached consented to participate, and 3 were excluded intraoperatively (2 because of difficulty with transvenous instrumentation, and

TABLE II Voltage and Current Recorded at Defibrillation Threshold for Leading (L) and Trailing (T) Edges of Pulses Used for Biphasic (pulses 1 and 2) and Monophasic Defibrillation in Two Groups of Patients

	Implantable Cardioverter-Defibrillator (chest closed)						Coronary Artery Bypass Grafting (chest open)					
	Biphasic				Monophasic		Biphasic				Monophasic	
	Pulse 1		Pulse 2				Pulse 1		Pulse 2			
	L	T	L	T	L	T	L	T	L	T	L	T
Voltage (V)	407 ± 101	140 ± 38	141 ± 34	50 ± 14	516 ± 117	182 ± 45	418 ± 108	142 ± 38	148 ± 43	51 ± 14	536 ± 147	184 ± 55
Current (A)	5.5 ± 1.5	2.0 ± 0.7	2.1 ± 0.6	0.7 ± 0.2	8.0 ± 4.0	2.6 ± 0.7	5.3 ± 1.5	1.7 ± 0.6	1.8 ± 0.5	0.6 ± 0.2	6.5 ± 1.6	2.3 ± 0.7

$p < 0.03$ for biphasic versus monophasic in all cases.

1 because of withdrawal by the surgeon owing to ST-segment depression during induction of anesthesia). Another 3 patients (2 ICD and 1 CABG) completed the protocol, but were excluded because electronic equipment malfunction resulted in no data.

One patient with CABG developed a sternal wound infection after surgery; another developed small, inferior Q waves and a peak serum creatine kinase MB fraction of 126 units (3.84%; perioperative myocardial infarction) after an episode of ventricular fibrillation in the cardiac intensive care unit. The maximal, peak serum, creatine kinase MB fraction in the other 8 patients with CABG was 60 units (5.17%), and all but the patient with the sternal wound infection were discharged within 15 days without other significant problems. Neither 2 perioperative complications (1 sternal wound infection and 1 perioperative myocardial infarction) were thought to be related to the protocol. One ICD patient was thought to have a pulmonary embolus (pleuritic chest pain and hemoptysis) after surgery, and 1 had a cardiac arrest leading to hypotension and transient renal failure. Five ICD patients had transient atrial fibrillation after surgery, 2 had transient worsening of heart failure, and 1 had a hematoma at the device pocket site. No complication was thought to be due to the protocol.

Defibrillation thresholds: The voltage and current recorded at defibrillation threshold for the leading and trailing edges of each pulse are presented in Table II. For each measurement, the mean values obtained for biphasic pulses were less ($p < 0.03$) than those obtained for monophasic pulses within each group of patients. For each waveform, there were no significant differences comparing these values in open-chest CABG patients with those in closed-chest ICD patients. Impedance was virtually identical for all pulses within each group of patients, but tended (not significant) to be greater when the chest was open.

The defibrillation thresholds expressed as total stored and delivered energy for biphasic and monophasic shocks are depicted in Figure 2, and individual data are presented in Table I. Energy needed for biphasic defibrillation was significantly less than that for monophasic defibrillation within each patient group. However, there were no significant differences when comparing the same waveform in open-chest CABG patients with that in closed-chest ICD patients.

The percentage of patients successfully defibrillated is plotted against the total stored energy for biphasic and monophasic shocks in Figure 3. Complete success (100%) using the combined data was achieved with ≤23.4 J for biphasic pulses, and 50% success needed 12.9 J; corresponding values for monophasic pulses were 42.4 and 22.0 J, respectively. Whereas biphasic shocks were more effective over the entire range of stored energies, the major advantage of biphasic shocks was observed for the tertile of patients with the highest defibrillation thresholds.

DISCUSSION

The 2 main findings of this study are that: (1) biphasic shocks for defibrillation using this particular nonthoracotomy system in humans result in a lower defibrillation threshold than do monophasic shocks, and this threshold was less than that previously reported with a similar lead configuration; and (2) this same result was obtained in 2 groups of subjects that differed in their mean left ventricular ejection fraction, whether their chests were opened or closed, and whether they were to undergo CABG or to receive an ICD.

Biphasic shocks were previously reported to be more effective than were monophasic ones in dogs[5] and humans[6,7] using epicardial patches. Furthermore, several nonthoracotomy systems in dogs[8–10] and humans[11] have shown a similar advantage of biphasic shocks. This study reports lower defibrillation thresholds with bi-

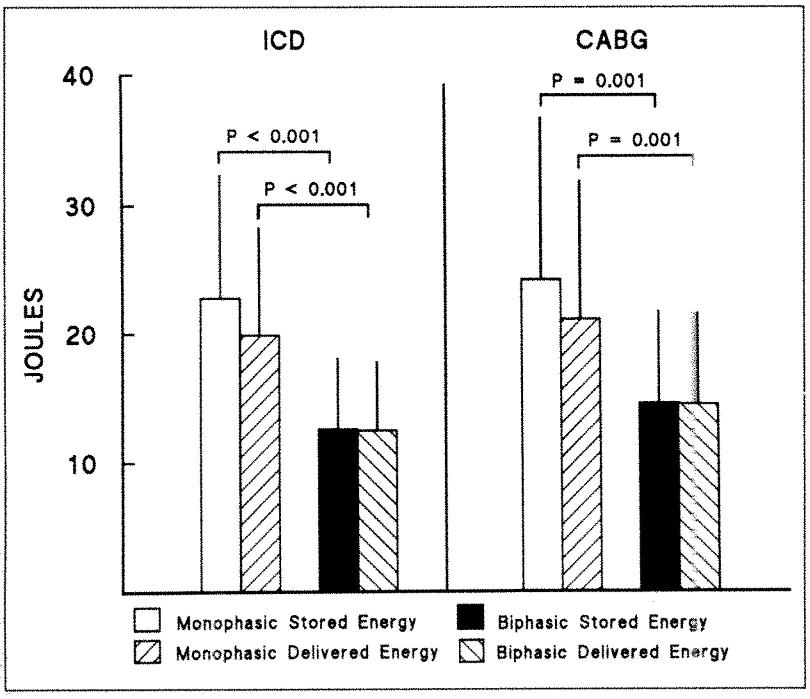

FIGURE 2. Defibrillation thresholds expressed as total stored and delivered energy for biphasic and monophasic shocks in 2 groups of patients. CABG = coronary artery bypass grafting; ICD = implantable cardioverter-defibrillator.

phasic shocks than with monophasic ones, and in both types of shock, the values obtained were much lower than those previously found using this nonthoracotomy lead system in humans. We believe this difference is due to positioning of the skin patch high in the left axilla, thus facilitating defibrillation of the base of the heart. The reasons for the reduced defibrillation thresholds with biphasic shocks are unknown, but several possibilities have been suggested.[12,13] Previous studies assessing biphasic cardiac stimulation[14] suggested that the first pulse of a biphasic shock repolarizes some cells and depolarizes others. The repolarization of cells results in reactivation of sodium channels to their resting state. These repolarized cells are more readily depolarized by the second pulse. This hypothesis implies that a biphasic shock can depolarize a larger mass of myocardium than can a monophasic one using the same amount of energy.

The 2 groups of experimental subjects in this study were distinctly different clinically. Therefore, it may be anticipated that the 2 groups would have different defibrillation thresholds. However, this was not the case. Counterbalancing factors affecting defibrillation threshold in the 2 groups may explain the unexpected similarities. Transthoracic impedance[15,16] and left ventricular mass[17] have been reported to have a role in defibrillation threshold. Having the chest open resulted in a slightly higher impedance that would have been expected to increase defibrillation threshold in patients with CABG. However, there was no difference in defibrillation threshold between CABG and ICD patients. This may imply that there is a counterbalancing factor increasing the defibrillation threshold in ICD patients. This factor may be a greater left ventricular mass in ICD patients. Cardiopulmonary bypass has been reported to have no effect on defibrillation threshold,[18] and therefore, although our patients with CABG were not on bypass, the presence of the venous cannula probably had no effect. Other factors reported to affect defibrillation threshold that were probably neutralized by the present protocol include duration of fibrillation,[19–21] implant time, catheter stability and adrenergic tone.[22,23]

Several antiarrhythmic drugs have been reported to affect defibrillation threshold.[23–31] Two patients in this study were receiving propranolol, which may have increased defibrillation threshold,[23] but 1 was in each of the 2 groups of patients. In addition, a patient in the ICD group was receiving amiodarone. However, chronic amiodarone treatment in humans has been reported to have no effects on defibrillation threshold.[30] One patient in the ICD group was receiving verapamil, which has been reported to increase defibrillation threshold,[31] and 4 in the CABG group were receiving diltiazem and 2 nifedipine. The effects of the latter 2 calcium antagonists on defibrillation threshold have not been reported. There was no difference in anesthetic use between the 2 groups. It is unlikely that antiarrhythmic drug therapy had any significant impact on the results of this study.

Study implications: Defibrillation thresholds noted in this study using a nonthoracotomy lead system were much less than those previously reported. The results suggest a wider applicability of this lead configuration, particularly in regard to the position of the skin patch. The difference between defibrillation thresholds for biphasic and monophasic shocks was noted in both groups of experimental subjects. Therefore, it is inferred that open-chest CABG patients who are not receiving an ICD may be a potential source of subjects for defibrillation research. However, further studies in larger groups are needed. This finding has important practical implications for research in humans on defibrillation using epicardial mapping.[13,32] The chest must be open to do the mapping, and as more ICDs are implanted using nonthoracotomy approaches, such studies will not be possible in most ICD patients. The use of patients with

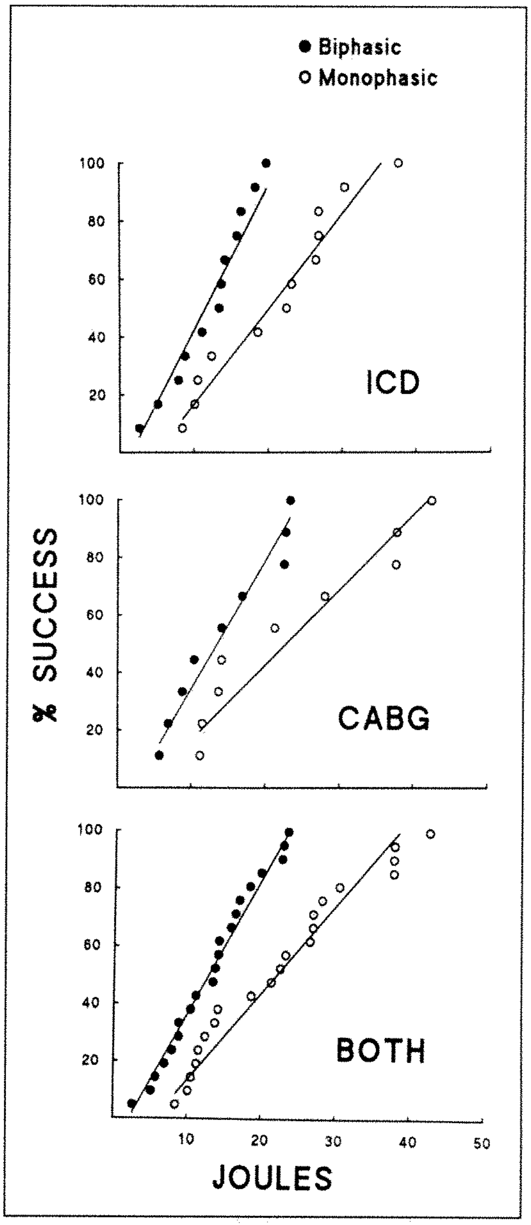

FIGURE 3. Plot of percent successful defibrillation versus total stored energy for biphasic and monophasic shocks. *Top and middle panels,* implantable cardioverter-defibrillator (ICD) and coronary artery bypass grafting (CABG) patients are shown separately, and *bottom,* all patients are combined. *Bottom,* linear regression was used to calculate 50% success of 12.9 J for biphasic shocks (r = 0.993) and 22 J for monophasic ones (r = 0.982).

CABG may be a suitable surrogate for epicardial mapping research during defibrillation.

REFERENCES

1. Jones DL, Klein GJ, Guiraudon GM, Sharma AD, Kallok MJ, Bourland JD, Tacker WA. Internal cardiac defibrillation in man: pronounced improvement with sequential pulse delivery to two different lead orientations. *Circulation* 1986; 73:484–491.

2. Jones DL, Klein GJ, Guiraudon GM, Sharma AD. Sequential pulse defibrillation in humans: orthogonal sequential pulse defibrillation with epicardial electrodes. *J Am Coll Cardiol* 1988;11:590–596.

3. Kowey PR, Friehling TD, Marinchak RA. Benefit/risk assessment in clinical research. *J Am Coll Cardiol* 1988;12:578–579.

4. Bigger TJ Jr. Future studies with the implantable cardioverter defibrillator. *PACE* 1991;14:883–889.

5. Dixon EG, Tang ASL, Wolf PD, Meador JT, Fine MJ, Calfee RV, Ideker RE. Improved defibrillation thresholds with large contoured epicardial electrodes and biphasic waveforms. *Circulation* 1987;76:1176–1184.

6. Winkle RA, Mead RH, Ruder MA, Gaudiani V, Buch WS, Pless B, Sweeney M, Schmidt P. Improved low energy defibrillation efficacy in man with the use of a biphasic truncated exponential waveform. *Am Heart J* 1989;117:122–127.

7. Bardy GH, Ivey TD, Allen MD, Johnson G, Mehra R, Greene LH. A prospective randomized evaluation of biphasic versus monophasic waveform pulses on defibrillation efficacy in humans. *J Am Coll Cardiol* 1989;14:728–733.

8. Chapman PD, Vetter JW, Souza JJ, Troup PD, Wetherbee JN, Hoffmann RG. Comparative efficacy of monophasic and biphasic truncated exponential shocks for nonthoracotomy internal defibrillation in dogs. *J Am Coll Cardiol* 1988;12:739–745.

9. Fain ES, Sweeney MB, Franz MR. Improved internal defibrillation efficacy with biphasic waveform. *Am Heart J* 1989;117:358–364.

10. Kavanagh KM, Tang ASL, Rollins DL, Smith WM, Ideker RE. Comparison of the internal defibrillation thresholds for monophasic and double and single capacitor biphasic waveforms. *J Am Coll Cardiol* 1989;14:1343–1349.

11. Bardy GH, Troutman C, Johnson G, Mehra R, Poole JE, Dolack GL, Kudenchuk PJ, Gartman DM. Electrode system influence on biphasic waveform defibrillation efficacy in humans. *Circulation* 1991;84:665–671.

12. Swartz JF, Jones JL, Jones RE, Fletcher R. Conditioning prepulse of biphasic defibrillator waveforms enhances refractoriness to fibrillation wavefronts. *Circ Res* 1991;68:438–449.

13. Zhow X, Knisley SB, Wolf PD, Rollins DL, Smith WM, Ideker RE. Prolongation of repolarization time by electric field stimulation with monophasic and biphasic shocks in open-chest dogs. *Circ Res* 1991;68:1761–1767.

14. Kavanagh KM, Duff HJ, Clark R, Robinson KV, Giles WR, Wyse DG. Monophasic versus biphasic cardiac stimulation: mechanism of decreased energy requirements. *Pace* 1990;13:1268–1276.

15. Sirna SJ, Ferguson DW, Charbonnier F, Kerber RE. Factors affecting transthoracic impedance during electrical cardioversion. *Am J Cardiol* 1988;62:1048–1052.

16. Dalzell GWN, Cunningham SR, Anderson J, Adgey AAJ. Electrode pad size, transthoracic impedance and success of external defibrillation. *Am J Cardiol* 1989;54:741–744.

17. Chapman PD, Sagar KB, Wetherbee JN, Troup PJ. Relationship of left ventricular mass to defibrillation threshold for the implantable defibrillator: a combined clinical and animal study. *Am Heart J* 1987;114:274–278.

18. Klein GJ, Jones DL, Sharma AD, Kallok MJ, Guiraudon GM. Influence of cardiopulmonary bypass on internal cardiac defibrillation. *Am J Cardiol* 1986; 57:1194–1195.

19. Mahmud R, Hsia P-W, Jolly SR, Jordan JC. Changes in transmyocardial impedance during prolonged ventricular fibrillation. Implications for current flow and delivered energy during DC countershock. *Am Heart J* 1990;120:334–339.

20. Bardy GH, Ivey TD, Allen M, Johnson G. A prospective, randomized evaluation of effect of ventricular fibrillation duration on defibrillation thresholds in humans. *J Am Coll Cardiol* 1989;13:1362–1366.

21. Winkle RA, Mead H, Ruder MA, Smith NA, Buch WS, Gaudiani VA. Effect of duration of ventricular fibrillation on defibrillation efficacy in humans. *Circulation* 1990;81:1477–1481.

22. Kallok MJ, Wibel FH, Bourland JD, Tacker WA Jr, Schollmeyer MP, Vanvleet JF. Catheter electrode defibrillation in dogs: threshold dependence on implant time and catheter stability. *Am Heart J* 1985;105:821–826.

23. Ruffy R, Schechtman K, Monje E, Sandza J. Adrenergically mediated variations in the energy required to defibrillate the heart: observations in closed- chest, nonanesthetized dogs. *Circulation* 1986;73:374–380.

24. Dorian P, Fain ES, Davy JM, Winkle RA. Lidocaine causes a reversible, concentration-dependent increase in defibrillation energy requirements. *J Am Coll Cardiol* 1986;8:327–332.

25. Kerber RE, Pandian NG, Jensen SR, Constantin L, Kieso RA, Melton J, Hunt M. Effect of lidocaine and bretylium on energy requirements for transthoracic defibrillation: experimental studies. *J Am Coll Cardiol* 1986;7:397–405.

26. Echt DS, Black JN, Barbey JT, Coxe DR, Cato E. Evaluation of antiarrhythmic drugs on defibrillation energy requirements in dogs. Sodium channel block and action potential prolongation. *Circulation* 1989;79:1106–1117.

27. Fain ES, Dorian P, Davy J-M, Kates RE, Winkle RA. Effects of encainide and its metabolites on energy requirements for defibrillations. *Circulation* 1986;73: 1334–1341.

28. Fram LH, Sheldon JH. Effect of recainam on the energy required for ventricular defibrillation in dogs as assessed with implanted electrodes. *J Am Coll Cardiol* 1988;12:746–752.

29. Hernandez R, Mann DE, Breckinridge S, Williams GR, Reiter MJ. Effects of flecainide on defibrillation thresholds in the anesthetized dog. *J Am Coll Cardiol* 1989;14:777–781.

30. Huang SKS, Tan de Guzman WL, Chenarides JG, Okike NO, Vander Salm TJ. Effects of long-term amiodarone therapy on the defibrillation threshold and the rate of shocks of the implantable cardioverter-defibrillator. *Am Heart J* 1991;122: 720–727.

31. Jones DL, Klein GJ, Guiraudon GM, Yee R, Brown JE, Sharma AD. Effects of lidocaine and verapamil on defibrillation in humans. *J Electrocardiol* 1991;24: 229–305.

32. Witkowski FX, Penkoske PA, Plonsey R. Mechanism of cardiac defibrillation in open-chest dogs with unipolar DC-coupled simultaneous activation and shock potential recordings. *Circulation* 1990;82:244–260.

Effects of Intravenous Milrinone on Left Ventricular Function in Ischemic and Idiopathic Dilated Cardiomyopathy

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Mouanodji Mbaissouroum, MD, and Derek G. Gibson, FRCP

M-mode echocardiography and Doppler were used to assess the effects of phosphodiesterase inhibition on subendocardial function in dilated cardiomyopathy, and in particular, to study interactions with both systolic and diastolic left ventricular function. Twelve adult patients with dilated cardiomyopathy were studied (6 ischemic in origin and 6 idiopathic), 7 of whom were being considered for cardiac transplantation. Cardiac index increased without significant change in heart rate or blood pressure. Longitudinal mitral ring motion, which had been uniformly reduced, increased markedly after intravenous milrinone. Left ventricular cavity size decreased, and shortening fraction, posterior wall thickness, and rates of posterior wall thickening and thinning increased markedly. Left atrial pressure decreased, and isovolumic relaxation time increased. However, the peak velocity and duration of the transmitral E wave increased, with no change in the A wave. Improved longitudinal (subendocardial) function was reflected by improved posterior wall dynamics, and early filling, possibly by augmentation of restoring forces. Thus, severely reduced subendocardial function in dilated cardiomyopathy is potentially reversible, with marked effects on systolic and diastolic function. These previously unrecognized actions of milrinone provide further evidence to justify its short-term use in supporting the severely depressed myocardium.

(Am J Cardiol 1993;71:203–209)

Milrinone, a peak III cyclic adenosine monophosphate-phosphodiesterase inhibitor, is known to have inotropic and vasorelaxant activity with effects on both systolic[1–3] and diastolic[4–6] left ventricular function. The compound is known to have favorable hemodynamic effects when administered intravenously in patients with severe ventricular disease.[7] The aim of this study was to define the basis for these effects on overall ventricular function in greater detail. In particular, we hoped to distinguish between the effects of the drug on the left ventricular minor axis from those on longitudinally directed fibers, which have been shown to be largely subendocardial in position by anatomic studies.[8] We also wanted to examine the diastolic effects of the drug in detail, attempting to separate any primary action on relaxation from changes secondary to improved systolic function.

METHODS

Patients: Twelve men (mean age 54 years, range 38 to 70) with severe ventricular disease (left ventricular end-diastolic dimension >6 cm and shortening fraction <20%) were studied. In 6 patients, the etiology was ischemic heart disease, and 3 had undergone coronary artery bypass surgery. In the remaining 6 patients, the etiology was idiopathic dilated cardiomyopathy. No patient was receiving concomitant, intravenous or oral, positive inotropic drugs, and long-acting nitrates, digoxin, β blockers and xamoterol were discontinued 48 hours before infusion of milrinone.

Study protocol: The study comprised a series of baseline measurements using M-mode and Doppler echocardiography, with simultaneous phonocardiography. An indwelling intravenous cannula was positioned in a peripheral vein before baseline measurements. Heart rate and sphygmomanometer cuff blood pressure were recorded, and baseline measurements were obtained twice at 10-minute intervals, during an infusion of saline solution. Each recorded value was the mean of 3 beats. The lower measurements of heart rate, mean blood pressure, short-axis end-systolic and end-diastolic cavity dimensions were within 15% of the higher value to ensure a stable baseline. Intravenous milrinone was administered within 15 minutes of the baseline measurements through a peripheral vein. A loading dose of 50 μg/kg was administered slowly over 10 minutes at a rate of 5 μg/kg/min, followed immediately by a constant infusion of 0.5 μg/kg/min. After 25 minutes of milri-

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none infusion, echocardiographic and Doppler measurements, heart rate and blood pressure variables were recorded, and on completion, the milrinone infusion was terminated.

Hemodynamic measurements: Heart rate, and systolic, diastolic and mean blood pressures were recorded. From the Doppler signal of aortic flow, and cross-sectional area of the left ventricular outflow tract, cardiac output was calculated, and cardiac, stroke and stroke work indexes derived.

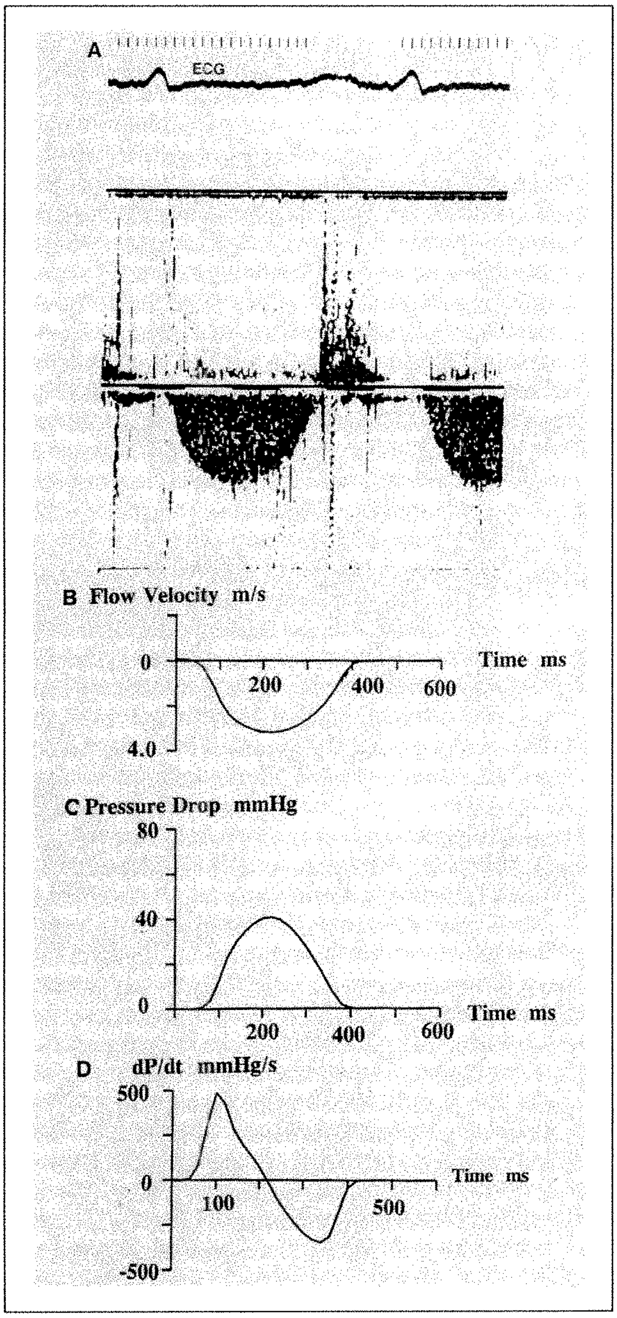

FIGURE 1. *A*, continuous-wave Doppler trace of mitral regurgitation. Full-scale deflection represents Doppler frequency shift of 16 kHz. *B*, digitized trace of mitral regurgitation. *C*, Calculated left ventricular/left atrial pressure drop derived from flow velocity data *(B)*. *D*, peak rates of left ventricular pressure increase and decrease from differential of pressure trace *(C)*. dP/dt = first derivative of ventricular pressure; ECG = electrocardiogram.

M-mode and cross-sectional echocardiography: M- mode and cross-sectional echocardiograms were obtained with the patient in the standard left lateral position, using an Advanced Technical Laboratory Imager Mk 300I with a 3 MHz mechanical transducer. M-mode echocardiograms were recorded with simultaneous electrocardiogram and phonocardiogram, on a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 10 cm/s. Aortic valve closure was considered as the onset of the first high-frequency vibration of the aortic component of the second heart sound recorded on the phonocardiogram, and was checked for validity with the aortic echogram and closure artefact on the Doppler recordings. Left ventricular internal cavity dimensions were measured at end systole (at aortic valve closure) and end diastole (onset of the QRS complex on the electrocardiogram) using leading-edge methodology, from the parasternal long-axis view, and shortening fraction was calculated. Posterior wall thickness was measured at end systole and end diastole. Isovolumic relaxation time was measured from aortic valve closure to the initial separation of the mitral cusps on the M-mode echogram, and mitral valve open time was measured as the total period from mitral cusp separation to closure at the onset of the succeeding systole. M-mode echocardiograms were digitized using a Terminal Display Systems TDS 20 digitizing tablet.[9] The extent of incoordinate relaxation was measured from the increase in transverse cavity dimension during isovolumic relaxation (expressed as a percentage of the total dimension change during the cardiac cycle) and also from the time interval from minimal cavity dimension to mitral valve opening. The peak rates of dimension increase and posterior wall thinning were also derived from the digitized traces.

Longitudinal axis measurements: An assessment of ventricular longitudinal function was obtained from measurement of mitral and tricuspid ring motion on long-axis M-mode echocardiograms. Excursion of the mitral ring was measured at the lateral and central fibrous body sites, and that of the tricuspid ring at the free wall.

Doppler echocardiography: We recorded Doppler signals with a Doptek Spectrascan and a 2 MHz transducer. Peak transmitral flow velocities were identified using continuous-wave Doppler from the apex, and were recorded in pulsed mode with a 3 mm gate and 250 Hz wall filter. The peak velocities of early (E wave) and atrial (A wave) transmitral flow were recorded, and the A/E ratio was derived. Acceleration and deceleration times of the E wave, and rapid filling duration (total E-wave duration) were measured. The time interval of aortic closure to the onset of transmitral flow was also recorded. Mitral and tricuspid regurgitant signals were identified and recorded in continuous-wave mode, and their durations were measured. The mitral and tricuspid regurgitation durations were subtracted from the RR interval to obtain the non–mitral regurgitation (left ventricular filling time) and non–tricuspid regurgitation (right ventricular filling time) intervals, respectively. The mitral regurgitation signal was digitized using a Terminal Display Systems TDS 20 digitizing tablet, and the peak left ventricular/left atrial pressure drop, and peak

TABLE I Hemodynamic Measurements

	Before Milrinone	After Milrinone	p Value
RR interval (ms)	606 ± 87	590 ± 55	NS
Heart rate (beats/min)	99 ± 13	102 ± 10	NS
Systolic BP (mm Hg)	109 ± 26	108 ± 25	NS
Diastolic BP (mm Hg)	67 ± 14	68 ± 14	NS
Mean BP (mm Hg)	81 ± 18	82 ± 17	NS
Cardiac output (L min^{-1})	3.2 ± 1.3	4.6 ± 1.7	0.003
Cardiac index (L min^{-1} m^{-2})	1.8 ± 0.7	2.5 ± 0.9	0.02
Stroke volume (ml)	32 ± 13	44 ± 17	0.005
Stroke index (ml m^{-2})	18 ± 7	24 ± 9	0.003
Stroke work (g m)	52 ± 31	69 ± 31	0.003
Stroke work index (g m/m^2)	29 ± 17	38 ± 17	0.02
Mean systolic ejection rate (ml s^{-1})	145 ± 48	189 ± 59	0.01
Peripheral resistance (Wood units)	27.8 ± 7.3	20.5 ± 6.5	0.02
Left atrial pressure (v wave) (mm Hg)	41 ± 11	28 ± 10	<0.05
Peak positive dP/dt (mm Hg s^{-1})	540 ± 225	640 ± 255	NS
Peak negative dP/dt (mm Hg s^{-1})	500 ± 150	570 ± 140	NS

BP = blood pressure; dP/dt = first derivative of left ventricular pressure.

TABLE II Echocardiographic Measurements

	Before Milrinone	After Milrinone	p Value
Left ventricular end-systolic dimension (cm)	6.5 ± 1.0	5.9 ± 1.1	<0.001
Left ventricular end-diastolic dimension (cm)	7.2 ± 1.1	6.8 ± 1.0	0.002
Shortening fraction (%)	10.4 ± 4.2	14.0 ± 5.9	0.005
End-diastolic posterior wall thickness (cm)	1.1 ± 0.2	1.2 ± 0.1	0.009
End-systolic posterior wall thickness (cm)	1.5 ± 0.3	1.7 ± 0.2	<0.001
Peak rate of posterior wall thickening (cm/s)	2.4 ± 1.0	3.6 ± 1.0	<0.001
Peak rate of posterior wall thinning (cm/s)	4.5 ± 1.8	8.3 ± 2.1	<0.001
Peak rate of minor axis dimension increase (cm/s)	7.9 ± 2.6	11.2 ± 2.8	<0.001
Epicardial excursion (mm)	2.1 ± 1.1	2.9 ± 2.6	NS
Isovolumic relaxation time (ms)	35 ± 25	60 ± 35	0.002
Aortic closure to onset of transmitral Doppler	70 ± 35	95 ± 30	0.001
% change in dimension before mitral valve opening (%)	7.9 ± 6.9	22.7 ± 20.7	<0.05
Minimum dimension to mitral valve opening (ms)	30 ± 15	50 ± 25	<0.05
Maximal amplitude of lateral site of mitral ring motion (cm)	0.7 ± 0.3	1.1 ± 0.3	<0.001
Maximal amplitude of central fibrous body motion (cm)	0.3 ± 0.3	0.6 ± 0.4	0.001
Maximal amplitude of right atrioventricular ring motion (cm)	1.3 ± 0.7	1.5 ± 0.6	NS

positive and negative first derivatives of left ventricular pressure were calculated (Figure 1). The height of the left atrial v wave was calculated as the difference between systolic arterial pressure and peak left ventricular/left atrial pressure drop. Cardiac output was measured from the flow velocity integral of a pulsed Doppler recording of aortic flow, and the cross-sectional area of the left ventricular outflow tract immediately beneath the valve. Records were obtained with simultaneous electrocardiogram and phonocardiogram at a paper speed of 10 cm/s.

Catecholamines: A 10 ml blood sample was obtained from the indwelling cannula into lithium-heparin tubes, before and after completion of the infusion of milrinone. Each sample was mixed and immediately centrifuged for 10 minutes. Plasma was decanted and frozen at –70°C until assay. Plasma catecholamines (epinephrine and norepinephrine) were measured by high-performance liquid chromatography with electrochemical detection.[10]

Statistical analysis: Throughout the study, 3 successive cardiac cycles were measured and mean values determined. All values are presented as mean ± SD. Differences between mean values before and after intravenous milrinone were compared by the paired Student's *t* test. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Hemodynamic measurements (Table I): Cardiac output increased (3.2 ± 1.3 vs 4.6 ± 1.7 liters/min; $p < 0.005$) without a significant change in either heart rate or mean blood pressure. Stroke volume and stroke work index increased significantly. Mean systolic ejection rate increased, and peripheral resistance decreased (both significantly). Left atrial pressure (v-wave height) decreased by a mean value of 13 mm Hg, whereas peak rates of pressure increase and reduction tended to increase (p = NS).

M-mode echocardiographic measurements (Table II): CHANGES IN MINOR-AXIS DYNAMICS AND WALL THICKNESS (FIGURE 2): End-systolic and end-diastolic cavity dimensions significantly decreased after milrinone ($p < 0.001$), with a significant increase in shortening fraction ($p < 0.01$). Thickness of the posterior wall increased at end-systole and end-diastole, and there were marked increases in the rate of posterior wall thickening and thinning, and in the peak rate of minor axis dimension increase (Figure 2). Excursion of the epicardium did not increase significantly.

ISOVOLUMIC INDEXES: Isovolumic relaxation time increased significantly when measured as aortic closure to both mitral valve opening and the onset of flow on Doppler. Measures of incoordinate relaxation increased, as may be expected with a longer isovolumic period.

CHANGES IN LONG-AXIS DYNAMICS (FIGURE 3): There was a marked increase in the maximal amplitudes of both mitral ring (Figure 3) and central fibrous body motion after milrinone, which had been uniformly reduced before infusion. However, motion of the tricuspid ring, which was not reduced before milrinone, did not change significantly.

Doppler indexes (Table III): There was no change in the peak velocity of the A wave of transmitral flow. However, despite the increase in isovolumic relaxation time, and the reduction in the left atrial v wave, peak E-wave velocity increased significantly ($p < 0.05$). The acceleration and deceleration times of the E wave increased ($p < 0.01$), so that the total rapid filling duration lengthened significantly. The duration of mitral regurgitation decreased, but that of tricuspid regurgitation was unchanged.

Catecholamines: There were no significant differences in plasma catecholamines before and after intravenous milrinone. Epinephrine levels were within the normal range (before 0.81 ± 0.75 nmol/liter, and after 0.63 ± 0.67 [p = NS]; normal range 0.03 to 1.31), but norepinephrine levels were high before and after milrinone (before 11.25 ± 4.46 nmol/liter, and after 10.31 ± 4.48; normal range 0.35 to 5.67). Thus, no observed hemodynamic effects could be attributed to drug-induced catecholamine release.

DISCUSSION

Milrinone is a bipyridine phosphodiesterase III inhibitor that promotes cyclic adenosine monophosphate-catalyzed phosphorylation of sarcolemmal calcium channels. It is known to have both inotropic and vasorelaxant activity in humans, with effects on systolic[1-3] and diastolic[4-6] function. We wanted to define its actions in greater detail to clarify its role as a potentially useful agent in circulatory support.

Systolic effects of milrinone: Cardiac output increased almost entirely due to increased stroke volume. Blood pressure was unaltered, so that stroke work index increased and peripheral resistance decreased. These changes occurred with reductions in left atrial pressure and left ventricular end-diastolic dimension (i.e., in both components of preload), and are thus entirely in accordance with the known dual action of the drug as both a positive inotropic agent and an arterial vasodilator. Peak first derivative of left ventricular pressure, derived from the mitral regurgitation trace, did not change significantly; this quantity is affected by both actions of the

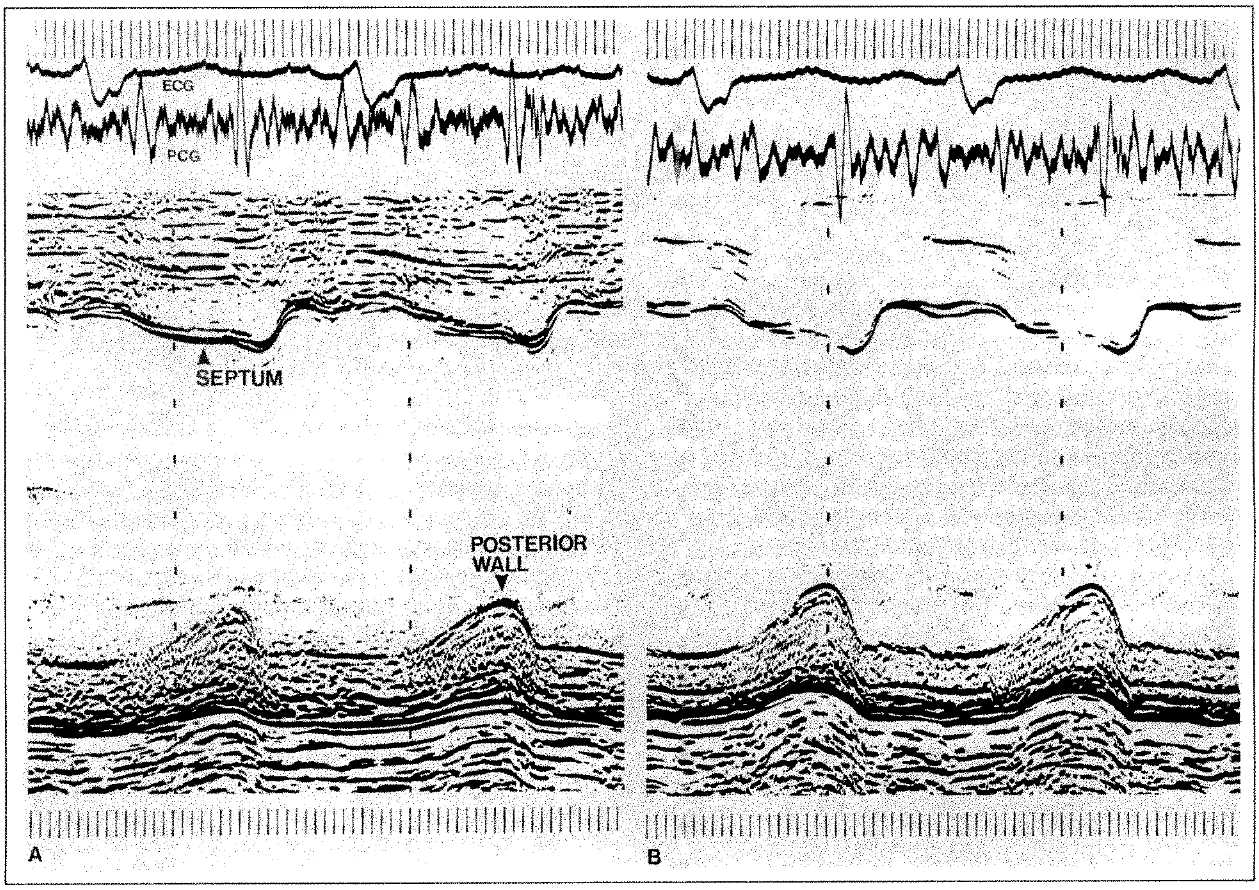

FIGURE 2. M-mode echocardiograms of left ventricular cavity obtained at level of tips of mitral leaflets before *(A)* and after *(B)* administration of intravenous milrinone. Endocardial surfaces of septum and posterior wall are shown. Records were obtained with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). Note increased amplitude of posterior wall motion and rate of thinning, and reduced end-systolic cavity dimension.

drug, increasing with a positive inotropic effect and decreasing with reduced preload. It appears likely that these 2 effects were balanced. Stroke volume increased because end-systolic cavity dimensions decreased proportionately more than those at end-diastole. This increase in the amplitude of wall motion was apparent from examining both short and long axes. In the short axis, it manifested itself as a marked increased in the extent of systolic wall thickening. Epicardial excursion was unaltered after milrinone, which makes it very unlikely that the increase in wall thickening was due to circumferential fiber shortening. Therefore, it must have been caused by the fattening of longitudinally directed fibers. Because myocardium is effectively incompressible, fattening in the transverse direction is the necessary consequence of longitudinal fiber shortening. In any individual patient, its extent can be deduced from the interrelations between transverse cavity dimensions, epicardial motion and wall thickening.[11] Since the apex of the ventricle does not move with respect to a transducer on the chest wall, changes in the extent of long-axis shortening are entirely due to motion of the mitral

TABLE III Doppler Measurements

	Before Milrinone	After Milrinone	p Value
A wave (m/s)	0.26 ± 0.23	0.28 ± 0.16	NS
E wave (m/s)	0.76 ± 0.26	0.83 ± 0.28	<0.05
A/E ratio	0.44 ± 0.36	0.50 ± 0.21	NS
E-wave acceleration time (ms)	55 ± 20	75 ± 20	0.006
E-wave deceleration time (ms)	75 ± 20	100 ± 25	0.006
E-wave acceleration (g)	1.45 ± 0.65	1.25 ± 0.50	<0.05
Rapid filling duration (ms)	135 ± 40	175 ± 30	0.003
Mitral regurgitation duration (ms)	380 ± 65	360 ± 50	0.01
Left ventricular filling time (ms)	215 ± 75	230 ± 60	NS
Tricuspid regurgitation duration (ms)	425 ± 75	355 ± 135	NS
Right ventricular filling time (ms)	195 ± 70	250 ± 150	NS
Left ventricular ejection time (ms)	220 ± 40	230 ± 35	NS

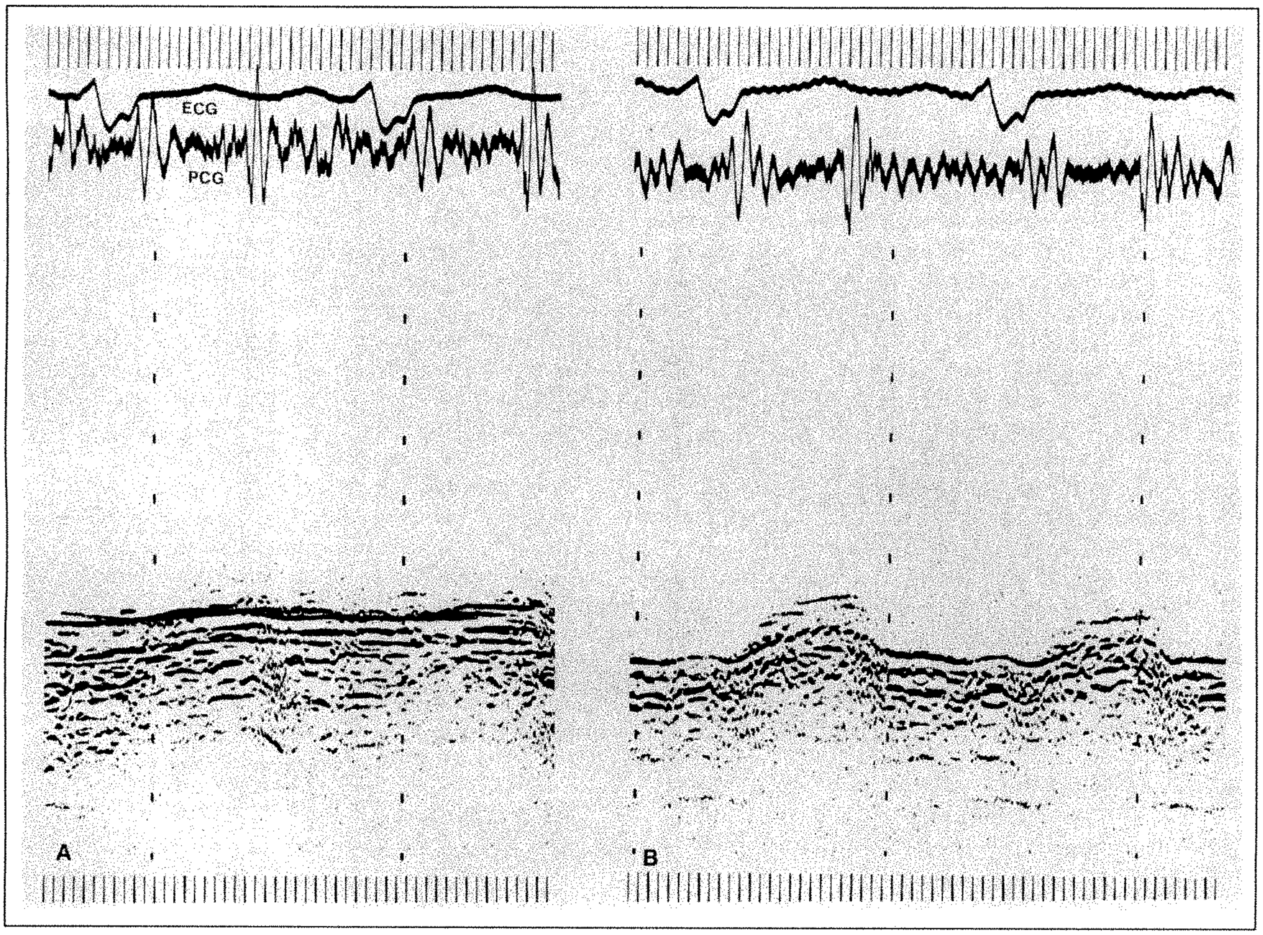

FIGURE 3. M-mode echocardiogram of lateral aspect of mitral annulus, reflecting mitral ring motion, before *(A)* and after *(B)* intravenous milrinone, recorded with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). Note marked reduction in ring motion, typical of dilated cardiomyopathy before milrinone, and increased systolic shortening of long axis after.

valve ring. Reduced mitral ring motion is recognized in dilated cardiomyopathy,[12] and the amplitude of this motion in our patients was reduced in control conditions and normalized by milrinone. The relative change was significantly greater than that in the minor axis. Motion of the right atrioventricular ring was only minimally reduced compared with in normal subjects,[13–15] and did not change significantly with milrinone. Therefore, we deduce that the changes in cavity volume were due in large part to the systolic effect on longitudinally directed fibers; not only did they lead directly to longitudinal shortening, but also contributed in a major way to the systolic increase in wall thickness underlying the reduction in minor axis.

Diastolic effects of milrinone: Left atrial pressure decreased and isovolumic relaxation increased. The duration of the rapid filling phase and peak E-wave velocity both increased, whereas A-wave velocity remained unchanged. Therefore, the increased stroke volume entered the ventricle in early rather than late diastole. It is now known that the acceleration of transmitral flow is due to the pressure gradient between the atrium and ventricle. Thus, peak acceleration of early diastolic flow can only be maintained when early diastolic left atrial pressure decreases, if there is a corresponding reduction in effective left ventricular pressure. There is increasing evidence to suggest that early diastolic left ventricular pressure is directly related to end-systolic cavity size. In normal subjects, early diastolic pressures may even be negative to atmospheric when end-systolic volume is low.[16,17] Thus we would expect the reduced end-systolic volume after milrinone to be associated with a reduction in early diastolic ventricular pressure, which explains how early diastolic flow velocities increased. A second effect contributing to the increase in the early diastolic time-velocity integral was prolongation of both acceleration and deceleration times. In control conditions, values of deceleration time were well within the range reported by Appleton et al[18] as being diagnostic of restrictive ventricular physiology. Deceleration time lengthened toward normal with milrinone. The improvement in restrictive physiology was presumably another result of a smaller end-systolic volume causing lower diastolic pressures, thus increasing operating compliance as the result of the curvilinear form of the left ventricular pressure–volume relation.

Significance of changes in left ventricular long-axis function: If this analysis is correct, it points to a pivotal role of long-axis shortening underlying the favorable effects of milrinone on the dilated left ventricle. Anatomic studies have shown the following 3 components of musculature arranged longitudinally: the papillary muscles, and fibers within the ventricular wall, dominantly subendocardially and to a lesser extent subepicardially.[8] Subendocardial fibers are particularly at risk in patients with dilated cardiomyopathy, both from the direct effects of any large or small vessel coronary artery disease, and from the indirect effects of raised left ventricular diastolic pressures. Both can lead to local ischemia and thus dysfunction. We believe the primary action of milrinone was on these fibers, increasing the extent of their shortening, and thus lowering effective left ventricular early diastolic pressure and increasing stroke volume.

Study limitations: Changes in the left ventricular minor axis were assessed using M-mode echocardiography, which has obvious disadvantages in studying overall left ventricular function. However, we excluded from the study patients with left ventricular aneurysms and obvious nonuniformity of cavity shape. The M-mode cursor was guided from the cross-sectional display, and patients served as their own control. Finally, our experimental design did not depend on using minor-axis measurements as indicators of overall function, but specifically to assess changes in dimension and wall thickening at midcavity level. Doppler-based estimates of left ventricular stroke volume depend on both stroke distance and cross-sectional area of the aorta or outflow tract.[19,20] There is no general agreement as to the exact site at which the latter should be measured; subaortic and aortic regions have both been used.[21,22] Furthermore, when cardiac output is reduced, aortic cusp opening may be incomplete, suggesting that aortic root diameter may overestimate the effective area of the column of blood leaving the ventricle. Although these limitations may cast doubt on the reliability of absolute measures of stroke volume, they are unlikely to affect directional changes in individual patients, where effective cross-sectional area is unlikely to change. Our estimates of left atrial pressure were indirect. We used the difference between peak systolic arterial pressure and peak atrioventricular pressure reduction. Thus, the calculated left atrial pressure is likely to have approximated to the v wave of the pressure pulse and will have been physiologically significant as a determinant of early diastolic left ventricular filling. The height of the v wave has only an indirect relation to end-diastolic pressure. We suggest that these values also decreased, on the basis of an increase in left ventricular isovolumic relaxation time,[23] and even more significantly, a reduction in end-diastolic dimension. The technique of determining peak rates of increase or decrease in pressure from the continuous-wave Doppler trace of functional mitral regurgitation is new[24] and has not been specifically validated in patients with dilated cardiomyopathy.

Conclusions: The data suggest a unitary mechanism of action of milrinone and that its diastolic effects are the direct mechanical consequence of its actions in systole on longitudinally directed subendocardial fibers. These properties may be of benefit for short-term use in patients with advanced ventricular disease in need of circulatory support.

REFERENCES

1. Jaski BE, Fifer MA, Wright RF, Braunwald E, Colucci WS. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure: dose-response relationships and comparison to nitroprusside. *J Clin Invest* 1985;75:643–649.

2. Timmis AD, Smyth P, Monaghan M, Walker L, Daly K, McLeod AA, Jewitt DE. Milrinone in heart failure: acute effects on left ventricular systolic function and myocardial metabolism. *Br Heart J* 1985;54:36–41.

3. Ludmer PL, Wright RF, Arnold JMO, Ganz P, Braunwald E, Colucci WS. Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique. *Circulation* 1986;73:130–137.

4. Monrad ES, McKay RG, Baim DS, Colucci WS, Fifer MA, Heller GV, Royal HD, Grossman W. Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone. *Circulation* 1984;70:1030–1037.

5. Piscione F, Jaski BE, Wenting GJ, Serruys PW. Effect of a single oral dose of milrinone on left ventricular diastolic performance in the failing human heart. *J Am Coll Cardiol* 1987;10:1294–1302.

6. Krams R, McFalls E, van der Giessen WJ, Serruys PW, Verdoun PD, Roelandt J. Does intravenous milrinone have a direct effect on diastolic function? *Am Heart J* 1991;121:1951–1955.

7. Biddle TL, Benotti JR, Creager MA, Faxon DP, Firth BG, Fitzpatrick PG, Konstam MA, Krebs C, Walton L, Kershner RP, Jacobsen J, Luczkowec CA, Montenaro MJ, Tandon PK, Fitzpatrick S, Schwartz RP Jr. Comparison of intravenous milrinone and dobutamine for congestive heart failure secondary to either ischemic or dilated cardiomyopathy. *Am J Cardiol* 1987;59:1345–1350.

8. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981;45:248–263.

9. Gibson DG, Brown D. Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* 1973;35:1141–1149.

10. Bouloux PMG, Perrett D, Besser GM. Methodological considerations on the determination of plasma catecholamines by high-performance liquid chromatography with electrochemical detection. *Ann Clin Biochem* 1985;22:194–203.

11. Dumesnil JG, Shoucri RM, Laurenceau J-L, Turcot J. A mathematical model of the dynamic geometry of the intact left ventricle and its application to clinical data. *Circulation* 1979;59:1024–1034.

12. Keren G, Sonnenblick EH, LeJemtel TH. Mitral annulus motion. Relation to pulmonary venous and transmitral flows in normal subjects and in patients with dilated cardiomyopathy. *Circulation* 1988;78:621–629.

13. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. *Am Heart J* 1984;107:526–531.

14. Jones CJH, Raposo L, Gibson DG. Functional importance of the long axis dynamics of the human left ventricle. *Br Heart J* 1990;63:215–220.

15. Hammarström E, Wranne B, Pinto FJ, Puryear J, Popp RL. Tricuspid annular motion. *J Am Soc Echocardiogr* 1991;4:131–139.

16. Nikolic S, Yellin EL, Tamura K, Vetter H, Tamura T, Meisner JS, Frater RWM. Passive properties of canine left ventricle: diastolic stiffness and restoring forces. *Circ Res* 1988;62:1210–1222.

17. Suga H, Goto Y, Igarashi Y, Yamada O, Nozawa T, Yasumura Y. Ventricular suction under zero source pressure for filling. *Am J Physiol* 1986;251:H47–H55.

18. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:757–768.

19. Christie J, Sheldahl LM, Tristani FE, Sagar KB, Ptacin MJ, Wann S. Determination of stroke volume and cardiac output during exercise: comparison of two-dimensional and Doppler echocardiography, Fick oximetry, and thermodilution. *Circulation* 1987;76:539–547.

20. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man. Clinical validation. *Circulation* 1983;67:593–602.

21. Fisher DC, Sahn DJ, Freidman MJ, Larson D, Valdes-Cruz LM, Horowitz S, Goldberg SJ, Allen HD. The effect of variations on pulsed Doppler sampling site on calculation of cardiac output: an experimental study in open-chest dogs. *Circulation* 1983;67:370–376.

22. Ihlen H, Amlie JP, Dale J, Forfang K, Nitter-Hauge S, Otterstad JE, Simonsen S, Myhre E. Determination of cardiac output by Doppler echocardiography. *Br Heart J* 1984;51:54–60.

23. Mattheos M, Shapiro E, Oldershaw PJ, Sacchetti R, Gibson DG. Non- invasive assessment of changes in left ventricular relaxation by combined phono-, echo-, and mechanocardiography. *Br Heart J* 1982;47:253–260.

24. Chen C, Rodriguez L, Guerrero L, Marshall S, Levine RA, Weyman AE, Thomas JD. Noninvasive estimation of the instantaneous first derivative of left ventricular pressure using continuous-wave Doppler echocardiography. *Circulation* 1991;83:2101–2110.

Comparison of Transthoracic and Transesophageal Echocardiography for Detection of Abnormalities of Prosthetic and Bioprosthetic Valves in the Mitral and Aortic Positions

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Two-dimensional echocardiography is the diagnostic procedure of choice for evaluation of prosthetic valve abnormalities. However, transthoracic echocardiography (TTE) may be limited owing to acoustic shadowing and poor acoustic windows. Some of these limitations may be overcome by transesophageal echocardiography (TEE). One hundred twenty-six patients with 148 prosthetic valves (113 bioprostheses and 35 mechanical devices) were studied by M-mode and 2-dimensional TTE and TEE. Prosthetic valve morphology was confirmed by surgery or autopsy in all cases; 124 prostheses were classified as diseased (33 endocarditis, 8 thrombi, and 83 degeneration defined as leaflet thickening >3 mm with restricted motion) and 24 as normal. Prosthetic valve endocarditis and thrombi were correctly identified by TTE in 12 of 33 (36%) and 1 of 8 (13%) prostheses, respectively, but could be diagnosed by TEE in 27 of 33 (82%; p <0.001) and 8 of 8 (100%; p <0.01), respectively. Compared with TTE, TEE had a higher sensitivity for morphologic prosthetic valve abnormalities in patients with either bioprostheses (88 [87%] vs 66 [65%] of 101 prostheses; p <0.01) or mechanical devices (19 [83%] vs 5 [22%] of 23 prostheses; p <0.01) and in patients with a prosthesis in either the aortic (49 [77%] vs 32 [50%] of 64; p <0.01) or mitral (58 [97%] vs 39 [65%] of 60; p <0.001) position. Overall, sensitivity and specificity were 57 and 63%, respectively, for TTE, and 86 and 88%, respectively, for TEE. TEE is superior to TTE in the correct identification of morphologic prosthetic valve abnormalities, and should be used in patients with suspected prosthetic valve malfunction and negative TTE.

(Am J Cardiol 1993;71:210–215)

Transthoracic 2-dimensional echocardiography (TTE) is the diagnostic procedure of choice for the evaluation of prosthetic valves. However, TTE can be limited in patients with poor acoustic window, and prostheses may create artifacts preventing sufficient image quality. The addition of Doppler has a valuable role in a comprehensive investigation by providing complementary hemodynamic and anatomic information.[1–7] In some cases with prosthetic valve abnormalities (such as small thrombi or vegetations, or the initial stage of tissue valve degeneration), however, the hemodynamic function of a diseased valve may be preserved for a period of time, and Doppler may reveal normal velocity parameters. In these patients, a sufficient image quality is needed to detect morphologic prosthetic valve abnormalities. Transesophageal echocardiogra-phy (TEE) provides a high resolution and an unobstructed view of cardiac structures,[8–11] and may be an important adjunct to TTE. In this study, we compared the findings visualized by TTE and TEE with those verified during reoperation or necropsy in 126 unselected patients with 148 prosthetic or bioprosthetic valves.

METHODS

Patients: The study comprised 126 consecutive patients (86 men and 40 women, age range 19 to 76 years) with 148 prostheses (78 in the aortic position, and 70 in the mitral position; 35 mechanical devices and 113 bioprostheses) examined between 1984 and 1990. Patients fulfilled the following selection criteria: (1) evaluation by both TTE and TEE on the same day; and (2) prosthetic valves had to be evaluated by subsequent anatomic inspection during reoperation (120 patients) or autopsy (6 patients).

Reoperation was due to valve replacement of either a diseased prosthesis (n = 104) or another diseased native heart valve (n = 22). Surgery or autopsy provided detailed anatomic description of all prostheses. Based on

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TABLE I Echocardiographic Findings in 83 Bioprostheses with Degeneration Proved by Surgery or Autopsy

	Transthoracic			Transesophageal		
	Normal	Questionable	Abnormal	Normal	Questionable	Abnormal
Aortic position (n = 41)	13	5	23 (56%)	7	4	30 (73%)
Mitral position (n = 42)	4	3	35 (83%)	0	0	42 (100%)
Total (n = 83)	17 (20%)	8 (10%)	58 (70%)	7 (8%)	4 (5%)	72 (87%)

Comparison of transthoracic and transesophageal echocardiography for total valves: chi-square 7.01, $p < 0.05$; for valves in aortic position: chi-square 2.84, $p = 0.24$; and for valves in mitral position: chi-square 7.64, $p < 0.05$.

TABLE II Echocardiographic Findings in 33 Prostheses with Endocarditis Proved by Surgery or Autopsy

	Transthoracic			Transesophageal		
	Normal	Questionable	Abnormal	Normal	Questionable	Abnormal
Aortic position (n = 21)	6	6	9	3	1	17
Bioprosthesis (n = 11)	2	3	6	1	0	10
Mechan. device (n = 10)	4	3	3	2	1	7
Mitral position (n = 12)	6	3	3	2	0	10
Bioprosthesis (n = 6)	2	2	2	1	0	5
Mechan. device (n = 6)	4	1	1	1	0	5
Total (n = 33)	12 (36%)	9 (27%)	12 (36%)	5 (15%)	1 (3%)	27 (82%)

Comparison of transthoracic and transesophageal echocardiography for total valves: chi-square 15.05, $p < 0.001$.
Mechan. = mechanical.

the macroscopic appearance, 124 prostheses were classified as diseased and 24 prosthetic valves as normal. For the purpose of this study, we focused on patients with prosthetic valve endocarditis, thrombi or degeneration; those with a paravalvular leak but without other morphologic prosthetic valve abnormalities were excluded, because most were examined before TEE Doppler technology was available.

Echocardiographic examination: Patients were studied by echocardiography 57 ± 16 days before reoperation or death, and all studies were evaluated by 2 independent physicians. In cases with initial discrepancies, both observers reevaluated the studies together, and a consensus was found. M-mode and 2-dimensional TTE were performed in standard conditions using 2.25 and 3.5 MHz phased-array transducers, and multiple parasternal, apical and subcostal image planes. For TEE, monoplane 3.5 and 5.0 MHz phased-array transducers mounted at the tip of a modified gastroscope (Diasonics, Hewlett-Packard, Acuson 128, ATL Ultramark 9) were used. All TEE was performed after administration of a local pharyngeal anesthetic without additional premedication.[12,13] Patients fasted for ≥4 hours and were examined in a left lateral decubitus position without complications. All TEE was performed primarily for diagnostic reasons. Informed consent was obtained from all patients before the examination.

Definition of prosthetic valve abnormalities: Morphology of all prostheses was rated as "normal," "abnormal" or "questionable"; "questionable" was used in cases in which no exact differentiation between normal and abnormal was possible owing to an insufficient image quality or other reasons. The echocardiographic criteria used to classify the various prosthetic valve diseases were as follows: (1) bioprosthesis degeneration, leaflet thickening >3 mm (with or without a flail portion due to partial leaflet rupture) associated with restricted leaflet motion; (2) valve endocarditis, sessile or pendulating masses attached to the valve and not inhibiting the motion of the leaflets or the occluder of the prostheses; and (3) thrombi, sessile valve-attached masses localized within the cage and usually associated with a restricted leaflet or occluder motion.

Statistics: For statistical analysis, the chi-square test was used. A p value <0.05 was considered significant. The detection of prosthetic valve malfunction by echocardiography compared with anatomic findings was de-

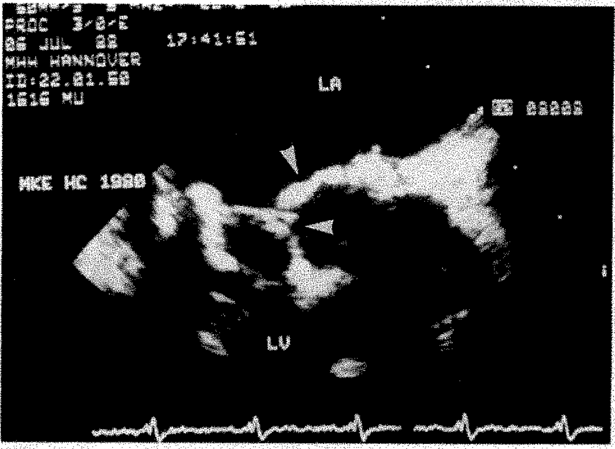

FIGURE 1. Transesophageal echocardiogram of patient with degenerated Hancock bioprosthesis in mitral position. Leaflets *(arrows)* show thickening and calcification due to degeneration. LA = left atrium; LV = left ventricle.

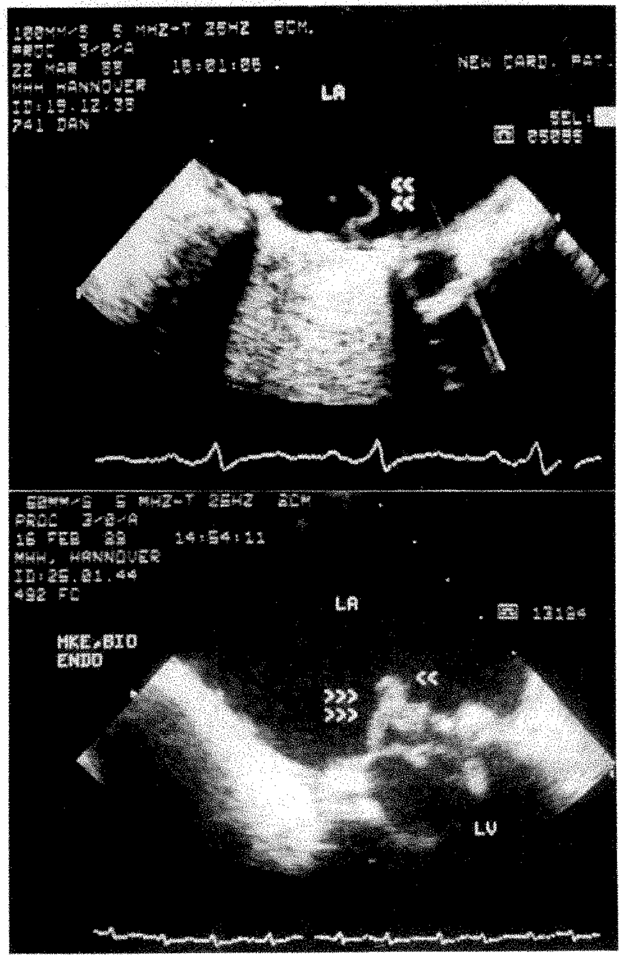

FIGURE 2. Transesophageal echocardiograms of 2 patients with infective endocarditis after mitral valve replacement. *Top,* Medtronic Hall mechanical device. Shadowing of mechanical device did not enable evaluation of atrial side of prosthesis by transthoracic approach. Transesophageal echocardiography clearly demonstrates pendulating vegetation *(arrows)* at atrial side of prosthesis. *Bottom,* bioprosthesis. Large vegetations *(arrows)* pendulating into left atrium (LA) in systole can be seen. LV = left ventricle.

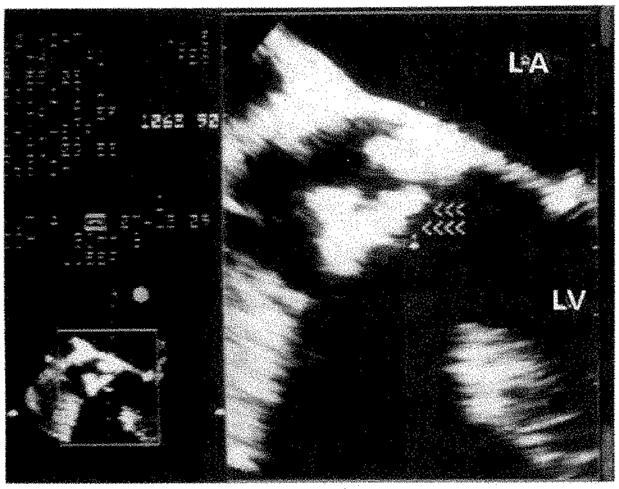

FIGURE 3. Transesophageal echocardiogram of patient with infective endocarditis after aortic valve replacement with bioprosthesis. Large vegetation *(arrows)* attached to leaflets can be seen. LA = left atrium; LV = left ventricle.

termined by calculating sensitivity and specificity as follows: For calculating sensitivity, only prostheses with definite echocardiographic abnormalities were considered to be abnormal; for specificity, only prostheses clearly without definite echocardiographic abnormal findings were considered to be normal.

RESULTS

Based on morphologic evaluation during surgery or autopsy, 33 prosthetic devices were diseased by infective endocarditis (21 in the aortic and 12 in the mitral position), 83 were degenerated (41 in the aortic and 42 in the mitral position), and 8 prosthetic valves had attached thrombi (2 in the aortic and 6 in the mitral position). Twenty-four prostheses were considered normal (14 in the aortic and 10 in the mitral position).

Bioprosthetic degeneration: The diagnostic accuracy of TTE and TEE in the detection of bioprosthesis degeneration is listed in Table I. TEE could correctly identify degeneration in a greater percentage of cases than could TTE (87 vs 70%; $p < 0.05$). However, this difference was not statistically significant for prostheses in the aortic position. In 3 of 7 cases in which TEE revealed false-normal findings, subsequent surgery showed a pinhole defect in 1 leaflet without further structural leaflet abnormalities; all 7 prostheses were in the aortic position. The sensitivity of both techniques was greater in patients with a bioprosthesis in the mitral position than in aortic devices ($p < 0.02$). A typical transesophageal echocardiographic image of a degenerated bioprosthesis is shown in Figure 1.

Endocarditis: Table II summarizes the diagnostic accuracy of TTE and TEE in the detection of prosthetic valve endocarditis. TEE had a significantly greater detection of vegetations than did TTE (82 vs 36%; $p < 0.001$) (Figures 2 and 3). Five of 6 patients with a

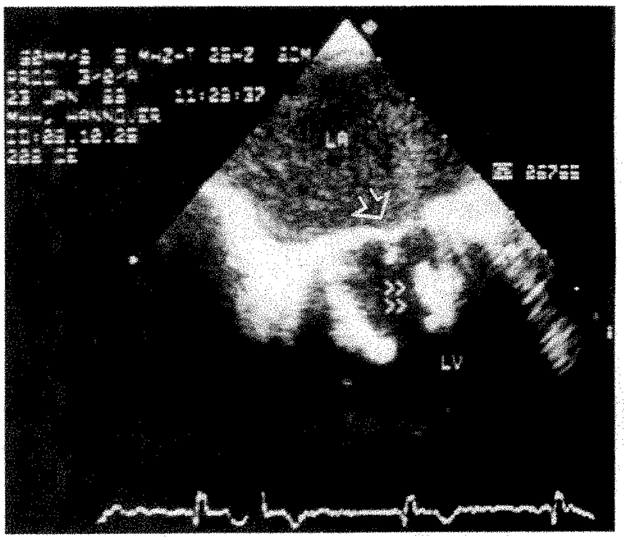

FIGURE 4. Transesophageal echocardiogram of patient with thrombus (*arrows;* subsequently proved by surgery) within cage of Hancock bioprosthesis in mitral position. Still-frame is obtained in end-systole, revealing that thrombus did not show movement with valve leaflets that are in closed position *(open arrow).* In left atrium (LA), spontaneous echo contrast can be seen. LV = left ventricle.

false-normal or "questionable" finding by TEE had a mechanical device or a prosthesis in the aortic position.

Thrombi: Whereas TEE could visualize prosthetic valve–attached thrombi in all 8 cases (2 mechanical devices in the aortic position, 1 bioprosthesis and 5 mechanical devices in the mitral position), TTE detected a thrombus only in 1 patient with a mechanical mitral prosthesis; in 2 other cases, the results of TTE were considered questionable (p <0.01). Figures 4 and 5 show typical transesophageal echocardiographic images of patients with thrombi attached to a bioprosthesis or mechanical device; in these cases, thrombi could not be detected by TTE.

Normal prostheses: Neither TTE nor TEE showed false-positive abnormalities in the 24 patients with 12 bioprostheses and 12 mechanical devices considered to be normal during anatomic inspection. However, a questionable result was obtained in 9 patients (38%) (6 in the aortic and 3 in the mitral position) by TTE and in 3 (13%) (2 in the aortic and 1 in the mitral position) by TEE. Overall, differences between TTE and TEE were not significant.

Sensitivity and specificity: The detection of the 3 types of prosthetic valve abnormalities in the evaluation of all 148 prostheses had a sensitivity and specificity of 57 and 63%, respectively, for TTE, and 86 and 88%, respectively, for TEE (p <0.001 for sensitivity; p = NS for specificity). In 17 of 124 diseased prostheses (14%), TEE was falsely negative or questionable; 15 of the 17 (88%) were localized in the aortic position, and 4 (24%) were mechanical devices. In contrast, TTE had a false-negative or questionable finding in 53 of 124 diseased prostheses (43%); in 32 (60%), the prosthesis was localized in the aortic position, and 18 (34%) were mechanical devices.

Aortic versus mitral position: In Table III, all diseased valves are analyzed separately for aortic and mitral position. In both positions, TEE resulted in a significantly greater detection rate of abnormalities than did TTE. In patients with a mitral prosthesis, TEE accurately revealed abnormalities in 58 of 60 cases (97%), whereas TTE was accurate in 39 (65%) (p <0.001). In regard to aortic valve prostheses, the detection rate of

TABLE III Detection of Prosthetic Valve Abnormalities by Transthoracic and Transesophageal Echocardiography; Dependency on Prosthetic Valve Position (105 patients with 124 diseased prosthetic valves)

	Echocardiographic Findings		
	Normal	Questionable	Abnormal
Mitral position (n = 60)			
TTE	14 (23%)	7 (12%)	39 (65%)
TEE	2 (3%)	0 (0%)	58 (97%)
Aortic position (n = 64)			
TTE	20 (31%)	12 (19%)	32 (50%)
TEE	10 (16%)	5 (8%)	49 (77%)

Comparison of TTE and TEE for valves in mitral position: chi-square 19.72, p <0.001; and in aortic position: chi-square 9.78, p <0.01.
TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

TABLE IV Detection of Prosthetic Valve Abnormalities by Transthoracic and Transesophageal Echocardiography; Dependency on Type of Prosthesis (105 patients with 124 diseased prosthetic valves)

	Echocardiographic Findings		
	Normal	Questionable	Abnormal
Bioprostheses (n = 101)			
TTE	22 (22%)	13 (13%)	66 (65%)
TEE	9 (9%)	4 (4%)	88 (87%)
Mechanical devices (n = 23)			
TTE	12 (52%)	6 (26%)	5 (22%)
TEE	3 (13%)	1 (4%)	19 (83%)

Comparison of TTE and TEE for bioprosthesis: chi-square 13.36, p <0.01; and for mechanical device: chi-square 17.14, p <0.001.
Abbreviations as in Table III.

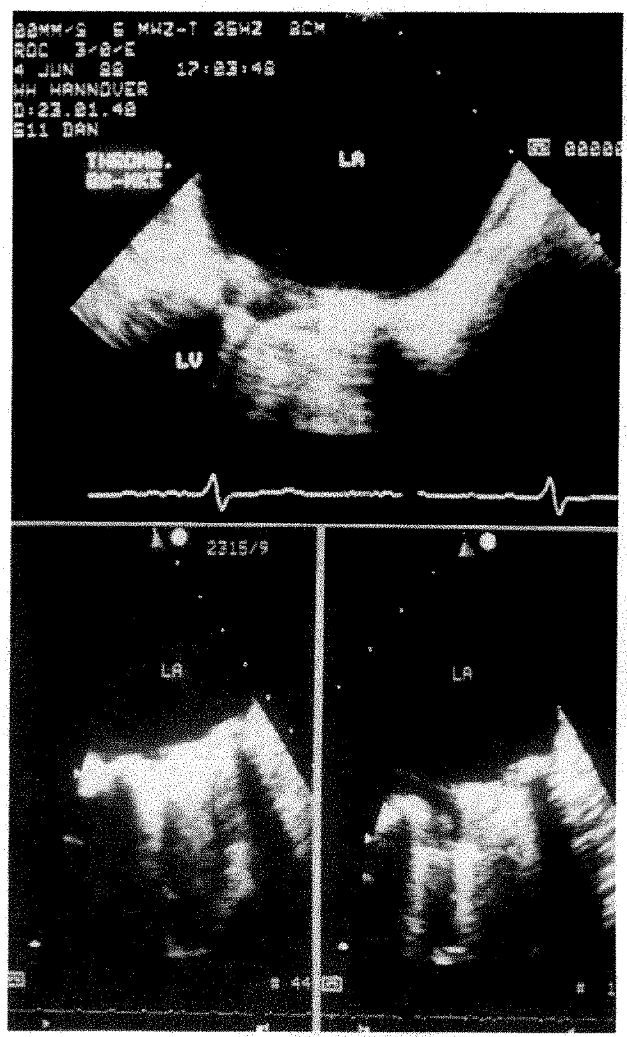

FIGURE 5. Transesophageal echocardiograms of 2 patients with thrombus (subsequently proved by surgery) attached to mechanical prostheses in mitral position. *Top,* Björk-Shiley prosthesis. In diastole, occluder of prosthesis shows only minimal opening due to restriction by thrombus. *Bottom,* bileaflet mechanical device. In systole *(left),* both occluders are in closed position. In diastole *(right),* only 1 occluder of prosthesis shows unobstructed opening; movement of other occluder is completely restricted by thrombus. LA = left atrium; LV = left ventricle.

abnormalities was reduced for both TTE (50%) and TEE (77%); however, the difference between TTE and TEE was significant ($p < 0.01$).

Bioprostheses versus mechanical devices: Table IV shows the comparison between TEE and TTE in regard to all diseased bioprostheses and mechanical devices. For both types of prostheses, TEE resulted in a significantly greater detection rate of abnormalities than did TTE. For mechanical devices, a particularly large difference between TEE and TTE was found (83 vs 22%; $p < 0.001$).

Interobserver variability: Interobserver variabilities were 11% ($n = 16$) for TTE and 6% ($n = 9$) for the TEE (p = NS). However, differences in the evaluation of prosthetic valve status were restricted to discrepancies between normal or abnormal and questionable, but not between normal and abnormal.

DISCUSSION

Assessment of prosthetic valve morphology by TTE may be difficult owing to limited acoustic windows and the highly reflective acoustic nature of prosthetic valve material. Whereas gross abnormalities can be detected in many patients, less flagrant abnormalities such as small vegetations and thrombi may be poorly appreciated, but may be all that is needed for emergent management decisions, such as urgent surgery. Mechanical devices produce multiple artifacts; this often prevents a reliable evaluation of prosthetic valve morphology.[14] Accordingly, the overall detection rate for vegetations or thrombi attached to mechanical devices was low (22%) in this series by TTE. This is in agreement with earlier reports,[15–18] although larger series with pathologic confirmation have not been available. TEE could considerably improve the diagnostic information: in 19 of 23 diseased mechanical devices (83%), TEE correctly identified vegetations or thrombi. This improved visualization by TEE can be explained by the following: (1) the unobstructed view provided by close approximation of the esophagus to the heart; (2) the ability to use higher frequency transducers, enabling the visualization of even small masses or masses with low echogenicity; and (3) the ability to evaluate the atrial surface of devices in the mitral position.[11,19–21] This latter point is of particular relevance, because thrombi or vegetations are usually attached at the atrial side of a mitral prosthesis, an area that is often inaccessible to TTE. Therefore, TEE appears to be the echocardiographic procedure of choice to evaluate mitral prosthetic valves (especially mechanical devices).

The diagnosis of aortic prosthetic valve abnormalities appears to be not as accurate by either TTE or TEE as that of mitral prostheses. Aortic prostheses (especially the left ventricular outflow tract side) may be partially obscured by artifacts created by the prosthetic ring when imaged by TEE in a short-axis plane. TEE could correctly diagnose abnormalities in only 77% of the diseased aortic prostheses (compared with 97% of mitral prostheses). However, TEE has increased diagnostic capabilities compared with TTE not only for mitral but also for aortic prostheses. Improved technology such as biplane or multiplane transesophageal echocardiographic probes will probably increase the diagnostic accuracy for evaluation of aortic prostheses.

Since bioprostheses consist of less reflecting material, many morphologic abnormalities can be identified by TTE.[6,11,15,17,22–25] However, this study shows that TEE also provides a higher detection rate for structural changes in bioprosthetic valves than does TTE. These findings are similar to those reported for native valve abnormalities.[12,26] TEE, when compared with TTE, led to an improvement in diagnostic accuracy of detecting vegetations and thrombi attached to bioprosthetic valves of ≥50%. This improvement was not as marked when evaluating bioprosthetic valve degeneration. Thickened and partially calcified tissue valves can usually be identified by TTE alone. However, isolated pinhole defects in bioprosthetic leaflets are nearly impossible to detect by either TTE or TEE without the additional use of color flow Doppler.[19]

Study limitations: Although one could argue that performing TTE before TEE favors the diagnostic accuracy of TEE, in the routine clinical setting, TTE should always be performed before TEE. Both techniques complement each other and are not competitive. Furthermore, in several cases, TTE was falsely negative and therefore misleading for TEE.

It may be difficult with either TEE or TTE to distinguish between bioprosthetic leaflet degeneration and small vegetative lesions. Although vegetative lesions often have chaotic unrestricted motion, and degenerative processes are usually associated with impaired valvular motion, in most patients, a definite distinguishing diagnosis can only be obtained when the clinical situation and history are noted. The situation is similar concerning the differentiation between thrombi and vegetations. Echocardiography may show that an abnormality is present, but cannot always determine the etiology.

Although it was not the purpose of this study to evaluate the additional diagnostic role of Doppler, the anatomic information provided by either TTE or TEE can be markedly enhanced by the hemodynamic findings provided by spectral and color flow Doppler.[7,11,19–21] For example, regurgitant lesions due to a paravalvular leak or a pinhole defect in a bioprosthetic leaflet may be missed by TTE and TEE, but can easily be detected by color Doppler flow mapping. In addition, pressure gradient measurements by Doppler are of major relevance for assessment of the severity of bioprosthetic valve degeneration. Both ultrasonic imaging and Doppler ideally should be performed for maximal diagnostic sensitivity.

Finally, this study is biased toward prosthetic valves with documented abnormalities. Only 24 prostheses were classified as normal by direct anatomic inspection. Thus, the study design does not enable the definitive determination of the specificity of TTE and TEE.

Conclusions and clinical implications: This study represents a large series of patients with proved morphologic abnormalities of prosthetic valves. TEE, when compared with TTE, has increased diagnostic capabilities for abnormalities of all types of prosthetic valves. It is especially prominent when evaluating mitral prostheses and, in particular, mechanical devices. The ability to examine the atrial side of mitral prostheses leads to improved diagnostic capabilities for the detection of thrombi and vegetations. Although the evaluation of aortic prostheses by monoplane TEE does not have as high a diagnostic accuracy as does that of mitral prostheses, advances in instrumentation such as biplane and multiplane TEE transducers should further improve the diagnostic accuracy of this technique. Although TEE is associated with some minor discomfort, it can be easily performed with minimal risk.[27,28] Therefore, patients with suspected malfunction of prosthetic valves could benefit from evaluation by both TTE and TEE. These techniques provide complementary information that together with clinical insight, can lead to proper management decisions.

Acknowledgment: We gratefully acknowledge the excellent technical assistance of Renate Schützenmeister in the echocardiographic laboratory.

REFERENCES

1. Veyrat C, Witchitz S, Lessana A, Ameur A, Abitbol G, Kalmanson D. Valvular prosthetic dysfunction. Localisation and evaluation of the dysfunction using the Doppler technique. *Br Heart J* 1985;54:273–284.

2. Panidis IP, Ross J, Mintz GS. Normal and abnormal prosthetic valve function as assessed by Doppler echocardiography. *J Am Coll Cardiol* 1986;8:317–326.

3. Sagar KB, Wann S, Paulsen WHJ, Romhilt DW. Doppler echocardiographic evaluation of Hancock and Björk-Shiley prosthetic valves. *J Am Coll Cardiol* 1986;7:681–687.

4. Chambers JB, Monaghan MJ, Jackson G, Jewitt DE. Doppler echocardiographic appearance of cusp tears in tissue valve prostheses. *J Am Coll Cardiol* 1987;10: 462–466.

5. Cooper DM, Stewart WJ, Schiavone WA, Lombardo HP, Lytle BW, Loop FD, Salcedo EE. Evaluation of normal and prosthetic valve function by Doppler echocardiography. *Am Heart J* 1987;114:576–582.

6. Alam M, Rosman HS, Lakier JB, Kemp S, Khaja F, Hautamaki K, Magilligan DJ, Stein PD. Doppler and echocardiographic features of normal and dysfunctioning bioprosthetic valves. *J Am Coll Cardiol* 1987;10:851–858.

7. Grigg L, Fulop J, Daniel L, Weisel R, Rakowski H. Doppler echocardiography assessment of prosthetic heart valves. *Echocardiography* 1990;7:97–114.

8. Frazin L, Talano JV, Stephanides L, Loeb HS, Kopel L, Gunnar RM. Esophageal echocardiography. *Circulation* 1976;54:102–108.

9. Schlüter M, Langenstein BA, Polster J, Kremer P, Souquet J, Engel S, Hanrath P. Transesophageal cross-sectional echocardiography with a phased array transducer system. Technique and initial clinical results. *Br Heart J* 1982;48:67–72.

10. Seward JB, Khandheria BK, Oh JK, Abel MD, Hughes RW, Edwards WD, Nichols BA, Freeman WK, Tajik AJ. Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. *Mayo Clin Proc* 1988;63:649–680.

11. Daniel LB, Grigg LE, Weisel RD, Rakowski H. Comparison of transthoracic and transesophageal assessment of prosthetic valve dysfunction. *Echocardiography* 1990;7:83–95.

12. Mügge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *J Am Coll Cardiol* 1989; 14:631–638.

13. Daniel WG, Mügge A, Martin RP, Lindert O, Hausmann D, Nonnast- Daniel B, Laas J, Lichtlen PR. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *N Engl J Med* 1991;324:795–800.

14. Boskovic D, Pechacek LW, Krajcer Z. Thrombosis of a Björk-Shiley aortic valve prosthesis diagnosed by two-dimensional echocardiography. *J Clin Ultrasound* 1983;11:165–169.

15. Cunha CLP, Guiliani ER, Callahan JA, Pluth JR. Echophonocardiographic findings in patients with prosthetic heart valve malfunction. *Mayo Clin Proc* 1980; 55:231–242.

16. Assanelli D, Aquilina M, Marangoni S, Morgagni GL, Visiolo O. Echo- phonocardiographic evaluation of the Björk-Shiley mitral prosthesis. *Am J Cardiol* 1986; 57:165–170.

17. Kotler MN, Mintz GS, Panidis I, Morganroth J, Segal BL, Ross J. Noninvasive evaluation of normal and abnormal prosthetic valve function. *J Am Coll Cardiol* 1983;2:151–173.

18. Mehlmann DJ, Talano JV. Detection of atrioventricular disc valve malfunction by two-dimensional echocardiography. *Am Heart J* 1982;104:1378–1381.

19. Nellessen U, Schnittger I, Appelton CP, Masuyama T, Bolger A, Fischell TA, Tye T, Popp RL. Transesophageal two-dimensional echocardiography and color Doppler flow velocity mapping in the evaluation of cardiac valve prostheses. *Circulation* 1988;78:848–855.

20. Taams MA, Gussenhoven EJ, Cahalan MK, Roelandt JRTC, van Herwerden LA, The HK, Bom N, de Jong N. Transesophageal Doppler color flow imaging in the detection of native and Björk-Shiley mitral regurgitation. *J Am Coll Cardiol* 1989;13:95–99.

21. Khandheria BK, Seward JB, Oh JK, Freeman WK, Nichols BA, Sinak LJ, Miller FA, Tajik AJ. Value and limitations of transesophageal echocardiography in assessment of mitral valve prostheses. *Circulation* 1991;83:1956–1968.

22. Effron MK, Popp RL. Two-dimensional echocardiographic assessment of bioprosthetic valve dysfunction and infective endocarditis. *J Am Coll Cardiol* 1983; 2:597–606.

23. Harston WE, Robertson RM, Friesinger GC. Echocardiographic evaluation of porcine heterograft valves in the mitral and aortic positions. *Am Heart J* 1978;96:448–457.

24. Schapira JN, Martin RP, Fowles RE, Rakowski H, Stinson EB, Frenche JW, Shumway NE, Popp RL. Two dimensional echocardiographic assessment of patients with bioprosthetic valves. *Am J Cardiol* 1979;43:510–519.

25. Forman MB, Phelan BK, Robertson RM, Virmani R. Correlation of two- dimensional echocardiography and pathologic findings in porcine valve dysfunction. *J Am Coll Cardiol* 1985;5:224–230.

26. Daniel WG, Schröder E, Mügge A, Lichtlen PR. Transesophageal echocardiography in infective endocarditis. *Am J Cardiac Imaging* 1988;2:78–85.

27. Daniel WG, Mügge A, Eschenbruch C, Lichtlen PR. Practicability of transesophageal echocardiography in conscious patients. In: Erbel R, Khandheria BK, Meyer J, Seward JB, Tajik AJ, eds. Transesophageal Echocardiography. Berlin-Heidelberg-New York: Springer Verlag, 1989;354–358.

28. Daniel WG, Erbel R, Kasper W, Visser CA, Engberding R, Sutherland GR, Grube E, Hanrath P, Maisch B, Dennig K, Schartl M, Kremer P, Angermann C, Iliceto S, Curtius J, Mügge A. Safety of transesophageal echocardiography—a multicenter survey of 10,419 examinations. *Circulation* 1991;83:817–821.

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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. *Am J Cardiol* 1984;53:900–915.

Chapter in Book: Cabot RC, White PD, Taussig HB, Levine SA, Wood P, Friedberg CK, Nadas AS, Hurst JW, Braunwald E. How to write cardiologic textbooks. In: Hope JA, ed. A Treatise on Disease of the Heart and Great Vessels. London: Yorke Medical Books, 1984:175–200.

Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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References: 1. Pickering TG, Hypertension and Lipid Trial Study Group. The use of 24-hour ambulatory monitoring in the assessment of antihypertensive therapy. Presented at the American Academy of Family Physicians 43rd Annual Assembly; September 24-29,1991; Washington, D.C. **2.** The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **3.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278–284.

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:
While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:
CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:
Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:
Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:
Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:
None known.

Cardiac Toxicity in Animals:
An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue / malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

No data are available in regard to overdosage in humans.
The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1990

Pfizer Roerig

Color Doppler Echocardiographic Determination of Mitral Regurgitant Flow from the Proximal Velocity Profile of the Flow Convergence Region

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Flow rate across an orifice can be determined from color Doppler echocardiographic maps of the flow convergence region proximal to the orifice. Different methods have been developed in vitro. The proximal velocity profile method was prospectively evaluated in patients with mitral regurgitation. Color Doppler echocardiography was performed in 74 patients before cardiac catheterization. The increasing velocities within the flow convergence region were determined in an apical plane on the straight line from the transducer to the leak; thus the proximal velocity profile was established and plotted on a nomogram. Instantaneous regurgitant flow rate was derived from the position of the resulting curve in relation to the nomogram's reference curves, which were derived from in vitro measurements. Regurgitant stroke volume was calculated as regurgitant flow rate • regurgitant velocity-time integral/regurgitant peak velocity, using additional continuous-wave Doppler. The 55 patients with angiographic regurgitation had a close association between regurgitant flow rate (0 to 600 ml/s) and angiographic grade (Spearman's rank correlation coefficient = 0.91; p <0.0001). Regurgitant flow rate did not overlap between grades ≤2+, 3+ and 4+. In 16 patients, regurgitant stroke volume by echocardiography correlated well with that by the angiography/Fick method (r = 0.88; SEE = 17.1 ml), with a regression line close to identity (y = 0.89x + 12.7 ml). The proximal velocity profile method enables determination of mitral regurgitant flow and estimation of regurgitant volume.

(Am J Cardiol 1993;71:217–224)

After the introduction of color Doppler echocardiography, assessment of mitral regurgitation was based on color flow maps of the regurgitant jet in the left atrium.[1–6] However, in addition to regurgitant flow rate, several other factors affect jet dimensions, including image quality, machine setup, driving pressure, wall adherence and fluid entrainment.[7–13] Recent investigations focused on the flow convergence region.[14–18] In this region on the ventricular side of the mitral valve, regurgitant flow concentrically accelerates from all sides toward the leak orifice. According to fluid dynamics, the flow pattern within the flow convergence region is predictable, and the velocity at discrete points of this region is linked to regurgitant flow rate. Color Doppler images of the flow convergence region provide such local velocity information. Different methods have been proposed to analyze these color flow maps of the flow convergence region and to calculate regurgitant flow rate.[15,19] In this study, we tested the proximal velocity profile method that has been developed by in vitro studies.[19]

METHODS

Study cohort: We prospectively studied 74 patients (31 women and 43 men, mean age 60.8 years, range 24 to 87) in our routine cardiac catheterization schedule. For 11 days, we randomly selected 2 patients per day (n = 22). Thereafter, we included 52 consecutive patients with mitral regurgitation found by color Doppler echocardiography. In 59 patients with a mitral regurgitant color jet, the etiology was as follows: 19 with coronary artery disease, 16 with rheumatic valve disease, 10 with mitral valve prolapse, 6 with bacterial endocarditis, 5 with dilated cardiomyopathy, 2 with aortic stenosis, and 1 with mitral prosthetic dysfunction. Thirty-seven patients had isolated mitral regurgitation, 13 additional mitral stenosis, 3 aortic regurgitation, 4 aortic stenosis, 1 combined aortic valve disease and 1 atrial septal defect. Fifty-one patients were in sinus rhythm, and 23 had atrial fibrillation.

Echocardiography: THEORETICAL AND EXPERIMENTAL BACKGROUND: The concept of the proximal velocity profile was used to estimate regurgitant flow rate. Its in vitro development has been described in detail elsewhere.[19] Given a jet-parallel scanning direction along the flow center line of the flow convergence, flow is parallel to the ultrasound beam so that local Doppler shift reflects absolute local velocity. The proximal velocity profile along this line is a hyperbolic curve that describes the convective acceleration toward the leak. Flow pattern

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within the flow convergence can theoretically be described by a flow net with stream and isopotential lines. The stream lines are independent of flow rate. Therefore, flow can change only parallel to the local velocity at any point of the flow net (i.e., the local velocity at any point is proportional to flow rate). Consequently, increases in regurgitant flow rate shift the proximal velocity profile curve upward, so that its position reflects regurgitant flow rate. (The curve is also influenced by orifice size, which is not known in vivo. This does not limit the method, because for a given maximal velocity [which is approximately the case in

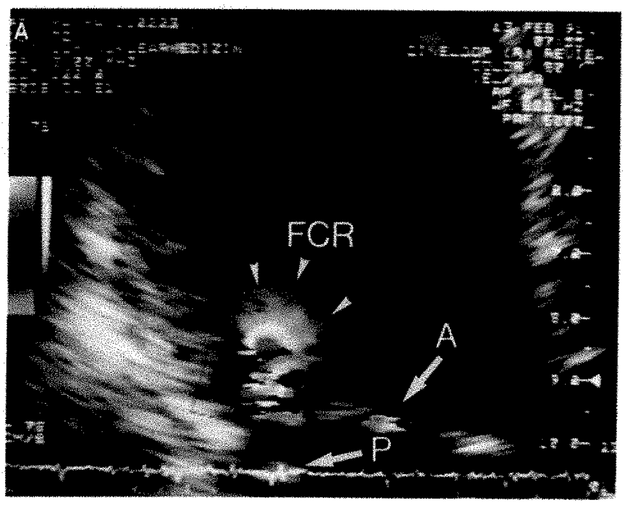
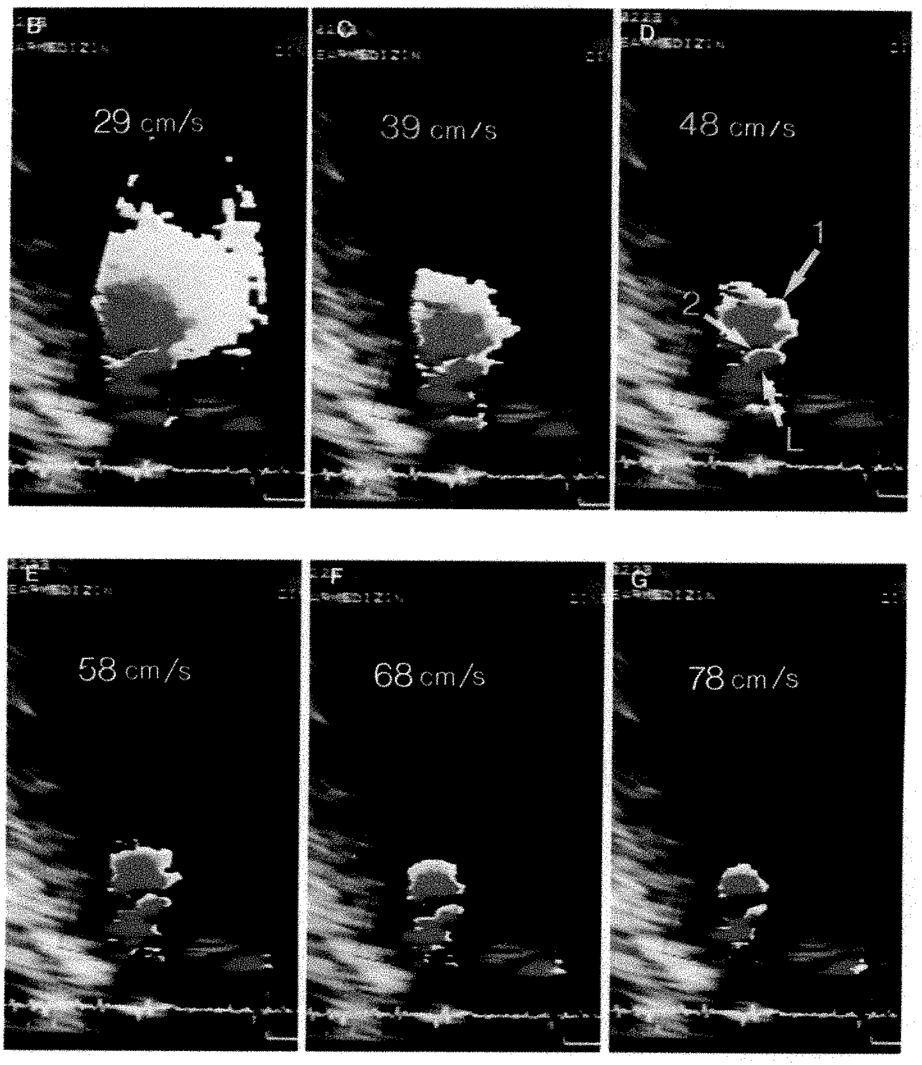


FIGURE 1. *A,* systolic color Doppler frame of patient with severe mitral regurgitation, 3-chamber view. *B to J,* postprocessing procedure for determination of proximal velocity profile. Special color map was used for clear delineation of alias contour. *Blue* was eliminated from standard map, so that *outer margin of yellow* represents alias contour. Beginning with color baseline in low position *(B),* it is shifted upward step by step. Thereby, alias velocity for downward direction increases progressively. A = anterior mitral leaflet; FCR = flow convergence region; L = function leak orifice; P = posterior mitral leaflet.



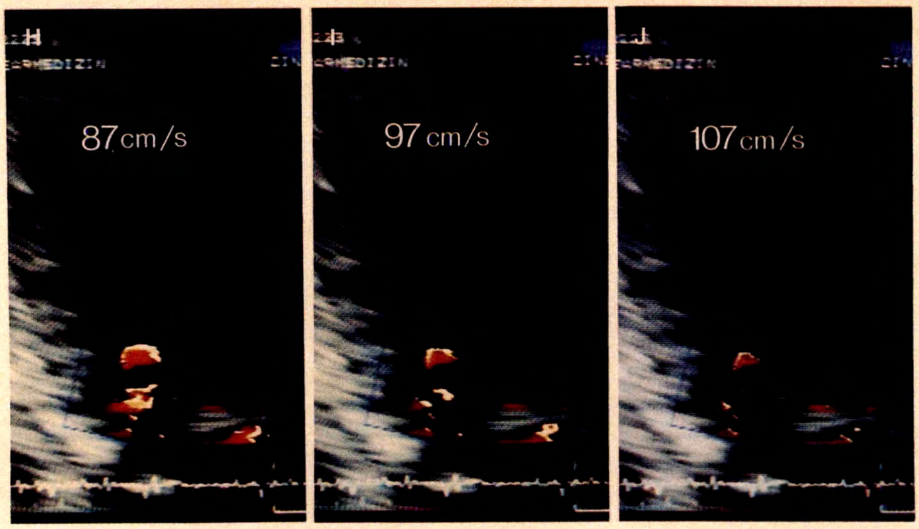
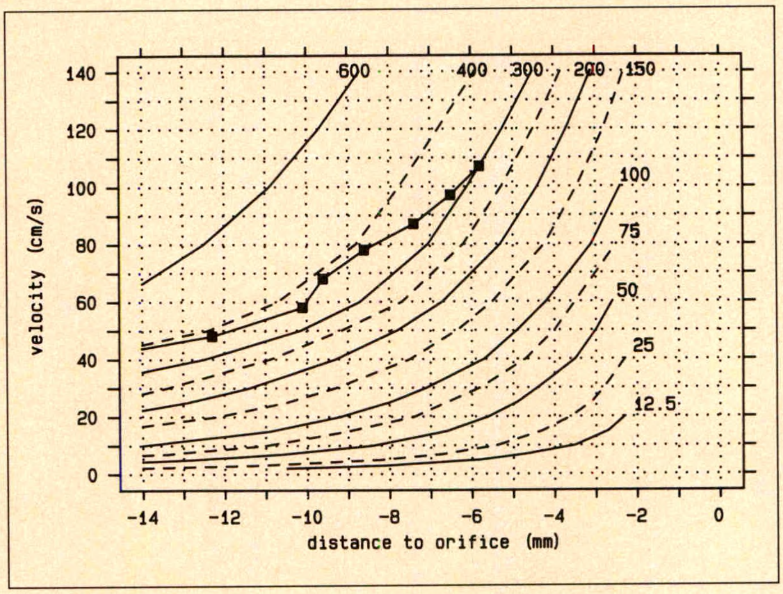


FIGURE 2. Nomogram for determination of regurgitant flow rate (ml/s) from proximal velocity profile curve. Curve resulting from example in Figure 1 is shown, representing flow rate of 350 ml/s.



mitral regurgitation], orifice size is linked to flow rate, so that the 2 need not be considered separately.) Flow rate is determined by analogy to reference curves. A nomogram consists of multiple reference curves from in vitro measurements. The proximal velocity profile curve of interest is plotted on this nomogram, and flow rate is estimated from the position of the curve in relation to the reference curves. (Theoretically, the more the in vivo geometry deviates from the ideal in vitro conditions, the more the in vivo flow net differs from that in vitro, and the more inaccurate is this analogy. These conditions include a planar orifice, no solid boundaries close to the orifice, and a circular orifice contour. However, in vitro studies[20] concerning the influence of these parameters on flow convergence suggest that the use of this nomogram in mitral regurgitation should not result in major inaccuracy. The nomogram originally ranged up to 300 ml/s[19]; for this study, it was extrapolated to 600 ml/s.)

IMAGING: All echocardiographic examinations were performed by the same experienced investigator <6 hours before catheterization (ATL ultramark 9 system, 3 MHz phased array and 2.25 MHz pencil scanhead). The

TABLE I Angiographic Grade

Investigator 2					
4+	0	0	0	4	6
3+	0	0	4	5	2
2+	0	1	7	2	0
1+	2	7	8	0	0
0+	19	7	0	0	0
	0+	1+	2+	3+	4+
	Investigator 1				

same apical window was used for recordings of flow convergence, left atrial color jets and continuous-wave Doppler spectra. The size of the color window was minimized to maintain the frame rate at a high level (generally >18 Hz). Pulse repetition frequency was 2,500 to 8,000 Hz at a wall filter of 200 to 600 Hz. The echocardiographic examination was recorded on VHS videotape.

COLOR DOPPLER ON-LINE ANALYSIS: The frame with the largest color-coded flow convergence signal was selected from the cineloop. The first frame after mitral valve closure and the last one before mitral valve open-

TABLE II Proximal Velocity Profile Measurements Versus Angiographic Grade

Angio	Q_{PVP} (ml/s)— n = 74	Reg. Vol./ Beat (ml)— n = 44	Reg. Vol./ Min (L/min)— n = 43	Reg. Index (L/min/m^2)— n = 41	Reg. Fraction (%)— n = 42	ROA$_{eff}$ (mm^2)— n = 44
0	0.74 (0–8)					
0/1+	14.2 (0–25)	6.4 (2.7–10.6)	0.41 (0.16–0.68)	0.3 (0.19–0.40)	8.9 (2.7–16.3)	3.6 (1.6–5.3)
1+	23 (8–58)	8.9 (2.6–20.0)	0.6 (0.16–1.60)	0.3 (0.1–0.7)	9 (3.1–16.7)	4.6 (1.2–10.0)
1+/2+	37 (8–88)	13.8 (1.9–25.0)	1.2 (0.15–2.90)	0.7 (0.1–1.8)	22 (2.4–39.0)	9.3 (3–18)
2+	48 (13–85)	14.9 (4.8–29.0)	1 (0.49–1.40)	0.52 (0.3–0.8)	21 (16–30)	8.9 (4.1–14.0)
2+/3+	92 (50–144)	25.6 (13–38)	2.2 (1.0–3.5)	1.3 (0.55–2.00)	35 (28–45)	20 (12–28)
3+	159 (125–217)	48.8 (25–64)	4.2 (2.4–6.0)	2.25 (1.2–3.4)	47 (33–55)	36 (30–47)
3+/4+	277 (169–400)	72 (48–92)	6.6 (3.6–10.3)	4 (1.8–7.7)	59 (42–74)	70 (30–110)
4+	360 (263–600)	91 (69–119)	8.2 (5.5–12.0)	4.9 (3.4–7.1)	69 (64–76)	81 (46–120)

Angio = angiographic grade; Q_{PVP} = regurgitant flow rate by proximal velocity profile method; Reg. = regurgitant; ROA$_{eff}$ = effective regurgitant orifice area; Vol. = volume.

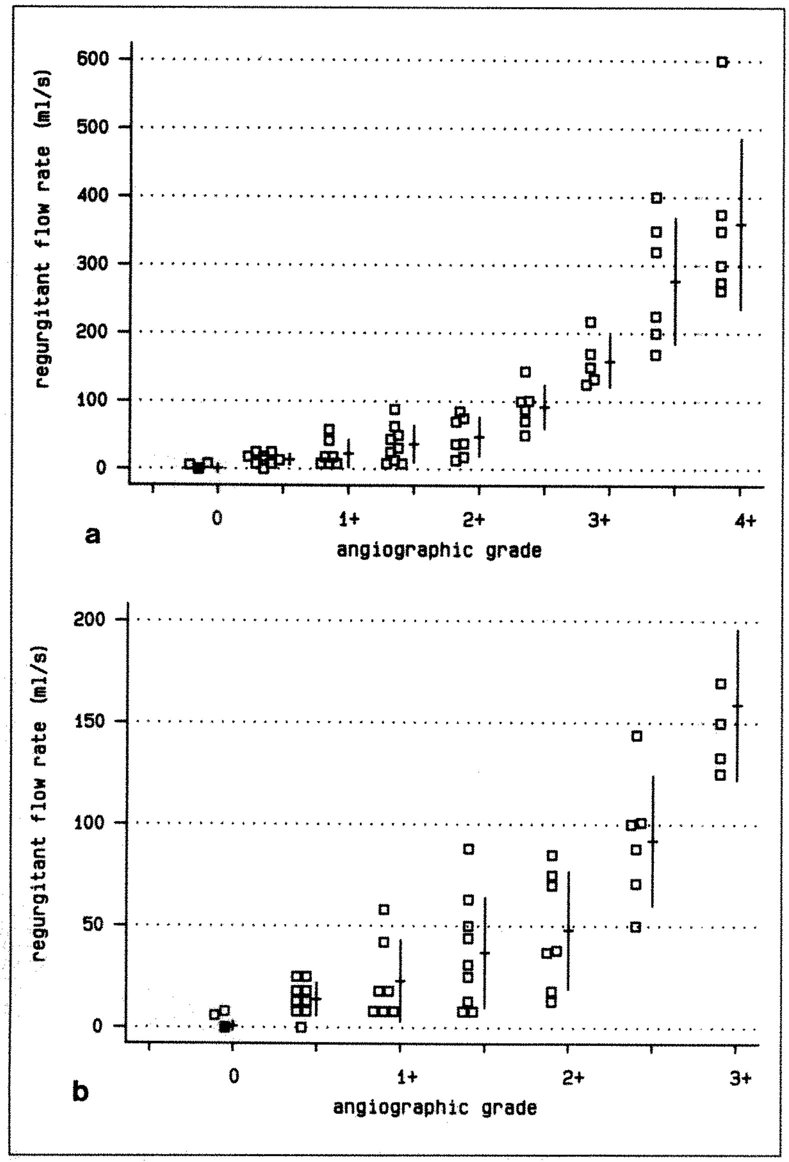


FIGURE 3. ***a,*** **regurgitant flow rate from proximal velocity profile versus angiographic grade. Each** ***open rectangle*** **represents 1 patient,** ***closed rectangle*** **represents 17 patients, and** ***vertical lines*** **indicate mean and SD. Patients with 1 grade difference between 2 angiographic investigators are plotted between 2 corresponding grades.** ***b,*** **regurgitant flow rate versus angiographic grade** ***(section of a),*** **illustrating range of mild and moderate mitral regurgitation.**

ing were excluded. Within the color-coded flow convergence area along the straight line from the transducer to the leak, discrete velocities were located by the alias method[19] using postprocessing color baseline shift (Figures 1 and 2). Velocities below the wall filter cutoff were excluded. The distance from the discrete velocity to the leak was measured on the screen. Thus, the proximal velocity profile across the flow convergence was established; it was plotted on the nomogram, and regurgitant flow rate was determined. Velocity profiles that crossed >1 reference curve were excluded. Three (sinus rhythm) to 5 (atrial fibrillation) beats were averaged.

Variability: In 24 randomly selected cases, the analysis was repeated by the same investigator and a blinded second investigator from redigitized video records >6 weeks after the first analysis.

CONTINUOUS-WAVE DOPPLER ANALYSIS: In 44 patients, the velocity-time integral and systolic peak velocity of the regurgitant continuous-wave Doppler spectra could be measured. For calculation of the regurgitant volume,

TABLE III Regurgitant Volumes Versus Angiographic Grade

	Regurgitant Index (liters/min/m²)		Regurgitant Fraction (%)	
Angio	Croft et al[23]	This Study	Rokey et al[24]	This Study
1+	0.6 ± 0.6 (0–3)	0.3 ± 0.2 (0.08–0.70)	22 ± 13 (13–36)	9 ± 6 (3–17)
2+	1.1 ± 0.9 (0–4)	0.5 ± 0.2 (0.3–0.8)	55 ± 13 (38–72)	21 ± 7 (15–30)
3+	2.1 ± 1.4 (0–4)	2.3 ± 0.8 (1.2–3.4)	49 ± 12 (40–67)	47 ± 9 (33–55)
4+	4.6 ± 2.3 (0.7–11.2)	4.9 ± 1.4 (3.4–7.1)	61 ± 13 (42–79)	69 ± 4 (64–76)

Studies from literature relating regurgitant index and fraction to angiographic grade in comparison with our results.
Angio = angiographic grade.

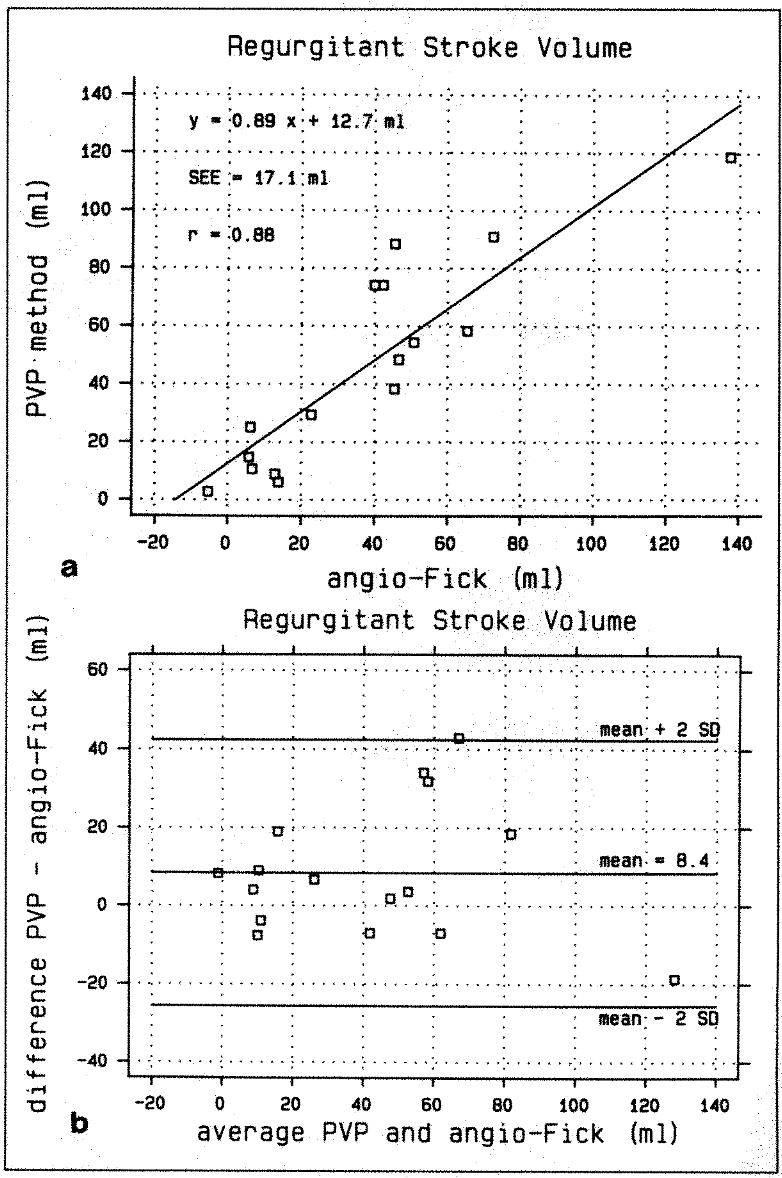


FIGURE 4. *a*, regression of regurgitant stroke volume by proximal velocity profile (PVP) method versus regurgitant stroke volume by angiography/Fick (angio-Fick) method. *b*, difference in PVP- and angio-Fick–derived regurgitant stroke volume *(y axis)* versus average of both *(x axis).*

TABLE IV Regurgitant Volumes from Literature

Investigators	Method	Reg. Vol./ Beat (ml)	Reg. Vol./ Min (L/min)	Reg. Fraction (%)
Sandler et al[25]	Sandler et al	3–156	0.18–14.00	
Morch et al[28]	^{133}Xenon infusion		0.01–12.00	
Blumlein et al[29]	Sandler et al	≤145		13–81
	Echocardiography (2-dimensional/Doppler)	0–101		0–81
	RNV			0–70
Jenni et al[30]	Sandler et al			≤77
Dittmann et al[31]	Sandler et al	28–185		24–79
	Echocardiography (2-dimensional/Doppler)	12–182		16–80
This study	PVP method	0–119	0–12	0–76

Summary of several other studies concerning regurgitant volumes and fraction without relation to angiographic grade compared with our results. Range of regurgitant volumes is in accordance with our measurement.

PVP = proximal velocity profile; RNV = radionuclide ventriculography; other abbreviations as in Table II.

we assumed the effective leak orifice area to be constant during regurgitation time. Given this assumption, the systolic time course of the regurgitant flow rate is proportional to that of the continuous-wave Doppler velocity. The frame with the largest flow convergence was assumed to reflect the peak of regurgitant flow, so that regurgitant stroke volume could be calculated as: regurgitant stroke volume = Q_{PVP} • velocity-time integral/peak velocity (continuous-wave Doppler), where Q_{PVP} = regurgitant flow rate determined from proximal velocity profile. We further calculated: regurgitant volume/min = heart rate • regurgitant stroke volume; regurgitant fraction = regurgitant volume/min/(regurgitant volume/min + cardiac output by Fick); and effective regurgitant orifice area = Q_{PVP}/peak velocity (continuous-wave Doppler).

Cardiac catheterization: ANGIOGRAPHIC GRADE: Standard biplane cineangiographic left ventriculography was performed (30° right anterior oblique and 60° left anterior oblique projections, and 40 to 45 ml of Iopromid at 18 ml/s). Mitral regurgitation was graded, according to Sellers et al,[21] independently by 2 blinded, experienced investigators (Table I).

REGURGITANT VOLUME: We determined mitral regurgitant stroke volume as angiographic[22] minus Fick-derived stroke volume. This was possible in 26 patients (angiogram with good contrast and without repeated premature ventricular contractions, and no aortic regurgitation or shunt lesion). Angiographic stroke volume of 3 successive beats was averaged in case of atrial fibrillation. In 6 patients without angiographic mitral regurgitation, the regurgitant volume was 3.1 ml (–18.9 to 27.6). In 16 patients with angiographic mitral regurgitation, regurgitant stroke volume could be measured by the proximal velocity profile method (as previously described).

Statistics: Results are expressed as mean ± SD (minimum–maximum). We used Spearman's rank correlation (regurgitant flow rate vs angiographic grade) and linear regression analysis (regurgitant stroke volumes by echocardiography vs angiography/Fick).

RESULTS

Presence of a flow convergence signal: A flow convergence signal, a color Doppler jet and angiographic mitral regurgitation were detected in 54 patients. Both false-positive patients (flow convergence signal with regurgitant flow rate = 6 and 8 ml/s, respectively, but no angiographic mitral regurgitation) had a color jet in the left atrium, whereas the only false-negative patient (angiographic grade 0/1+) did not.

Regurgitant flow rate: We found a close association between regurgitant flow rate (proximal velocity profile method) and angiographic grade (Figure 3 and Table II). In the 25 patients with angiographic regurgitation and interobserver agreement, regurgitant flow rate was significantly correlated to angiographic grade (Spearman's rank correlation coefficient = 0.91; $p < 0.0001$).

Regurgitant volume: Regurgitant volumes and fraction derived from the proximal velocity profile showed a close association to angiographic grade (Figure 4 and Table II). In 16 patients in whom all the necessary measurements could be obtained, there was a significant correlation between regurgitant stroke volume by the angiography/Fick method and that derived from the proximal velocity profile ($r = 0.88$, SEE 17.1 ml; regression line: $y = 0.89x + 12.7$ ml).

Variability: The correlations between the measurements were as follows: intraobserver — $r = 0.987$, SEE 21 ml/s, regression line $y = 0.994x + 2.16$ ml/s; and interobserver — $r = 0.984$, SEE 23.7 ml/s, regression line $y = 1.09x + 0.5$ ml/s.

DISCUSSION

Regurgitant flow rate and angiographic grade: The close association between regurgitant flow rate and angiographic grade validates the proximal velocity profile method for clinical use in mitral regurgitation. The values for regurgitant flow rate overlapped between grades 1+ and 2+, but they enabled discrimination of grade ≤2+ from ≥3+ and ≤3+ from 4+. Because of the wide range of regurgitant flow rate, moderate inaccuracy in its determination is unlikely to cause clinically relevant error. In these aspects, the proximal velocity profile method appears superior to the assessment of mitral regurgitation from the left atrial color jet dimensions,[1–4,6] where discrimination of grade ≤2+ from ≥3+ is not possible. Some studies showed overlapping jet areas between grades 1+ and 4+. The absolute values of jet dimensions for different angiographic grades are so close together that minor inaccuracy can result in clinically relevant error.

Quantitative reference measurements: MEASUREMENTS OF THIS STUDY: The regurgitant stroke volume by the proximal velocity profile method correlates well with that by the angiography/Fick method. The regression line was close to the line of identity, suggesting accurate absolute values of regurgitant stroke volume. We conclude that the absolute values of regurgitant flow rate are accurate, as well. It is unlikely that the calculation procedure from regurgitant flow rate to regurgitant stroke volume (previously described) may have corrected for a major error.

REGURGITANT VOLUMES BY OTHER METHODS: For grades 3+ and 4+, the results are in complete accordance with other studies[23,24] where regurgitant volumes were related to angiographic grade (Table III). Those studies determined regurgitant stroke volume as the difference between angiographic total stroke volume and forward stroke volume by the Fick or thermodilution method.[25] The inaccuracy of these measurements limits the value of this method in the individual case.[3,26] Consequently, negative values of regurgitant volume should be expected in some mild cases. The fact that those studies did not find any negative values suggests that the mean values for grades 1+ and 2+ were too high, which would explain the discrepancy with our results. However, our values may be too low in grades 1+ and 2+. Although this comparison does not confirm the absolute value in the individual case, it suggests that the proximal velocity profile method is unlikely to have a major systematic error. Table IV summarizes further studies.

Comparison with other flow convergence studies: Before the proximal velocity profile method, other investigators described the proximal isovelocity surface area method as a simple way to analyze color Doppler images of the flow convergence region.[15] (Only 1 discrete velocity is located within the flow convergence color map. This discrete velocity dimension is assumed for every point of a hemispheric isovelocity surface. Flow rate is calculated as $Q_{PISA} = A_{(v)} \cdot v$, where Q_{PISA} = flow rate by proximal isovelocity surface area method, $A_{(v)}$ = surface area of the assumed isovelocity hemisphere, and v = discrete velocity defining the isovelocity hemisphere. In vivo, a satisfactory correlation with invasive measurements has been shown for flow across ventricular septal defects[27] and mitral valve leaks.[17] Using this method, Bargiggia et al[17] found much greater regurgitant flow rates than we did. This discrepancy needs further clarification. However, the proximal velocity profile method results in more plausible absolute values. The proximal isovelocity surface area method has 2 limitations: Only 1 point of the flow convergence color map is analyzed. An overly simplistic model of the convergence flow net is used that is unrealistic, because hemispheres with a radius >15 to 20 mm do not fit between the ventricular walls and flow in the outflow tract. In contrast, the proximal velocity profile method represents a better use of the velocity information contained in the color map, because all points are considered where flow is parallel to the ultrasound beam. The analysis is restricted to a distance <15 mm proximal to the leak orifice.

Study limitations: A minor error in the measured distance from the alias contour to the leak orifice causes a considerable error in the resultant regurgitant flow rate. Figure 2 shows how a difference of 1 mm can easily cause a difference in regurgitant flow rate of 20%. This sensitivity to inaccurate distance measurement is an inherent limitation of any flow convergence method at present.[15,19] Therefore, in some patients, the difficulty in locating the leak orifice should be considered a source of inaccuracy. This is not a major limitation for the clinical use in mitral regurgitation, where even an error of 30% would not result in coarse clinical misinterpretation. When the functional leak orifice cannot be located precisely in the 2-dimensional color flow image, some additional information can be obtained from the color map; by increasing the alias velocity step by step (postprocess color baseline shift), the alias contour progressively contracts toward the functional leak orifice. In some cases, the second alias contour is seen, which enables an even closer localization (Figure 1).

REFERENCES

1. Yoshida K, Yoshikawa J, Yamaura Y, Hozumi T, Akasaka T, Fukaya T. Assessment of mitral regurgitation by biplane transesophageal color Doppler flow mapping. *Circulation* 1990;82:1121–1126.

2. Spain MG, Smith MD, Grayburn PA, Harlamert EA, DeMaria AN. Quantitative assessment of mitral regurgitation by Doppler color flow mapping: angiographic and hemodynamic correlations. *J Am Coll Cardiol* 1989;13:585–590.

3. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP. Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;75:175–183.

4. Becher H, Mintert C, Grube E, Lüderitz B. Classification of mitral regurgitation by color flow mapping (CFM). *Z Kardiol* 1989;78:764–770.

5. Omoto R, Yokote Y, Takamoto S, Kyo S, Ueda K, Asano H, Namekawa K, Kasai C, Kondo Y, Koyano A. The development of real-time two-dimensional Doppler echocardiography and its clinical significance in acquired heart diseases with special reference to the evaluation of valvular regurgitation. *Jpn Heart J* 1984;25:325–340.

6. Miyatake K, Izumi S, Okamoto M, Kinoshita N, Asonuma H, Nakagawa H, Yamamoto K, Takamiya M, Sakakibara H, Nimura Y. Semiquantitative grading of severity of mitral regurgitation by real-time two-dimensional Doppler flow imaging technique. *J Am Coll Cardiol* 1986;7:82–88.

7. Bolger AF, Eigler LN, Maurer G. Computer analysis of Doppler color flow mapping images for quantitative assessment of in vitro fluid jets. *J Am Coll Cardiol* 1988;12:450–457.

8. Maciel BC, Moises VA, Shandas R, Simpson IA, Beltran M, Valdes-Cruz LM, Sahn DJ. Effects of pressure and volume of the receiving chamber on the spatial distribution of regurgitant jets as imaged by color Doppler flow mapping. *Circulation* 1991;83:605–613.

9. Switzer DF, Yoganathan AP, Nanda NC, Woo Y-R, Ridgway AJ. Calibration of color Doppler flow mapping during extreme hemodynamic conditions in vitro: a foundation for a reliable quantitative grading system for aortic incompetence. *Circulation* 1987;75:837–846.

10. Simpson IA, Valdes-Cruz LM, Sahn DJ, Murillo A, Tamura T, Chung KJ. Doppler color flow mapping of simulated in vitro regurgitant jets: evaluation of the effects of orifice size and hemodynamic variables. *J Am Coll Cardiol* 1989;13:1195–1207.

11. Krabill KA, Sung H-W, Tamura T, Chung KJ, Yoganathan AP, Sahn DJ. Factors influencing the structure and shape of stenotic and regurgitant jets: an in vitro investigation using Doppler color flow mapping and optical flow visualization. *J Am Coll Cardiol* 1989;13:1672–1681.

12. Wranne B, Ask P, Loyd D. Quantification of heart valve regurgitation: a critical analysis from a theoretical and experimental point of view. *Clin Physiol* 1985;5:81–88.

13. Sahn DJ. Instrumentation and physical factors related to visualization of stenotic and regurgitant jets by Doppler color flow mapping. *J Am Coll Cardiol* 1988;12:1354–1365.

14. Okamoto M, Tsubokura T, Nakagawa H, Morichika N, Amioka H, Yamagata T, Hashimoto M, Tsuchioka Y, Matsuura H, Kajiyama G. The suction signal detected by color Doppler echocardiography in patients with mitral regurgitation: its clinical significance. *J Cardiol* 1988;18:739–746.

15. Recusani F, Bargiggia GS, Yoganathan AP, Raisaro A, Valdes-Cruz LM, Sung H-S, Bertucci C, Gallati M, Moises VA, Simpson IA, Tronconi L, Sahn DJ. A new method for quantification of regurgitant flow rate using color flow Doppler imaging of the flow convergence region proximal to a discrete orifice: in vitro study and initial clinical experience in patients with mitral insufficiency. *Circulation* 1991;83:594–604.

16. Yoshida K, Yoshikawa J, Yamaura Y, Hozumi T, Shakudo M, Akasaka T, Kato H. Value of acceleration flows and regurgitant jet direction by color Doppler flow mapping in the evaluation of mitral valve prolapse. *Circulation* 1990;81:879–885.

17. Bargiggia GS, Tronconi L, Sahn DJ, Recusani F, Raisaro A, di Servi S, Valdes-Cruz LM, Montemartini C. A new method for quantitation of mitral regurgitation based on color flow Doppler imaging of flow convergence proximal to regurgitant orifice. *Circulation* 1991;84:1481–1489.

18. Appleton CP, Hatle LK, Nellessen U, Schnittger I, Popp RL. Flow velocity acceleration in the left ventricle: a useful Doppler echocardiographic sign of hemodynamically significant mitral regurgitation. *J Am Soc Echo* 1990;3:35–45.

19. Giesler M, Stauch M. Color Doppler determination of regurgitant flow: from proximal isovelocity surface areas to proximal velocity profiles—an in vitro study. *Echocardiography* 1992;9:51–62.

20. Utsunomiya T, Ogawa T, Doshi R, Patel D, Quan M, Henry WL, Gardin J. Doppler color flow "proximal isovelocity surface area" method for estimating volume flow rate: effects of orifice shape and machine factors. *J Am Coll Cardiol* 1991;17:1103–1111.

21. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease. *Am J Cardiol* 1964;14:437–447.

22. Greene DG, Carlisle R, Grant C, Bunnell IL. Estimation of left ventricular volume by one-plane cineangiography. *Circulation* 1967;35:61–69.

23. Croft CH, Lipscomb K, Mathis K, Firth BG, Nicod P, Tilton G, Winniford MD, Hillis LD. Limitation of qualitative angiographic grading in aortic and mitral regurgitation. *Am J Cardiol* 1984;53:1593–1598.

24. Rokey R, Sterling LL, Zoghbi WA, Sartori MP, Limacher CM, Kuo LC, Quinones MA. Determination of regurgitant fraction in isolated mitral or aortic regurgitation by pulsed Doppler two-dimensional echocardiography. *J Am Coll Cardiol* 1986;7:1273–1278.

25. Sandler H, Dodge HT, Hay RE, Rackley CE. Quantitation of valvular insufficiency in man by angiocardiography. *Am Heart J* 1963;65:501–513.

26. Shah PM. Quantitative assessment of mitral regurgitation. *J Am Coll Cardiol* 1989;13:591–593.

27. Moises VA, Maciel BC, Hornberger LK, Murillo-Olivas A, Valdes-Cruz L, Sahn DJ, Weintraub RG. A new method for noninvasive estimation of ventricular septal defect shunt flow by Doppler color flow mapping: imaging of the laminar flow convergence region on the left septal surface. *J Am Coll Cardiol* 1991;18:824–832.

28. Morch JE, Klein SW, Richardson P, Froggatt G, Schwartz L, McLoughlin M. Mitral regurgitation measured by continuous infusion of ^{133}Xenon. *Am J Cardiol* 1972;29:812–816.

29. Blumlein S, Bouchard A, Schiller NB, Dae M, Byrd BF, Ports T, Botvinick EH. Quantitation of mitral regurgitation by Doppler echocardiography. *Circulation* 1986;74:306–314.

30. Jenni R, Ritter M, Eberli F, Grimm J, Krayenbühl HP. Quantification of mitral regurgitation with amplitude-weighted mean velocity from continuous wave Doppler spectra. *Circulation* 1989;79:1294–1299.

31. Dittmann H, Voelker W, Karsch K-R, Seipel L. Die Doppler-echokardiographische Quantifizierung des regurgitierenden Blutvolumens bei Patienten mit Mitralinsuffizienz. *Klin Wochenschr* 1989;67:940–945.

NEW INFORMATION

Now you can help increase survival and prevent hospitalizations in many early symptomatic heart failure patients with Left Ventricular Dysfunction

SOLVD

Results from the largest and longest heart failure trial to date are in. And they demonstrate that enalapril — usually in combination with conventional therapy* — is superior to conventional therapy alone in increasing survival and preventing hospitalizations in symptomatic mild-to-moderate heart failure with left ventricular dysfunction (LVD).[1]

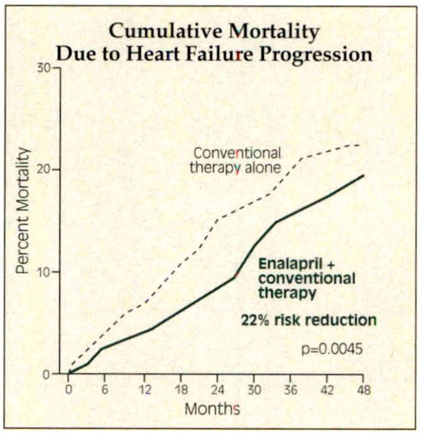
SOLVD — a 4-year survival study of enalapril in mild-to-moderate heart failure (n=2569)

The Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial, conducted by the NIH, evaluated 2569 heart failure patients (98% NYHA Classes I through III) with ejection fractions ≤0.35. These patients were selected from over 39,000 screened patients. (Another 4228 patients who were asymptomatic were selected for a second SOLVD trial and 6336 patients with ejection fractions <0.45 were included in a registry.) Diseases that excluded patients from enrollment in the Treatment Trial included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2.5 mg/dL), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis, and constrictive pericarditis.

This double-blind, placebo-controlled, multicenter trial lasted 4 years (average follow-up was 41.4 months). All patients received conventional therapy and were randomized to add either enalapril or placebo.

Patients live longer

SOLVD demonstrated a clear survival benefit for many of these symptomatic patients receiving enalapril compared with conventional therapy alone. All-cause mortality was reduced 11%. The largest mortality reduction occurred in deaths due to heart failure progression...a risk reduction of 22%.



Difference in mortality as early as 3 months

Mortality reductions with enalapril were observed as early as 3 months and throughout the entire study. The greatest benefit occurred during the first 24 months (19% reduction at the end of 24 months).

Patients hospitalized less

SOLVD demonstrated that enalapril reduced the number of hospitalizations for heart failure by 30% (p<0.001) — and that it reduced the number of readmissions by 33% (p<0.001).

The authors noted: for every 1000 heart failure patients similar to those in the study, 350 hospitalizations could be prevented over 3 years by adding enalapril.

The impact on your practice and your patients

By adding VASOTEC early to conventional therapy, you can help to significantly improve symptoms, increase survival, and prevent hospitalizations in many of your patients with symptomatic mild-to-moderate heart failure with LVD. The earlier you prescribe VASOTEC in appropriate patients, the sooner they may realize the benefits demonstrated in the SOLVD study.

VASOTEC®
(ENALAPRIL MALEATE)

In Symptomatic
Heart Failure,
Usually with
Diuretics
and Digitalis

---

*Diuretics (86% of patients in the enalapril group; 85% in the placebo group) and digitalis (66% of patients in the enalapril group; 68% in the placebo group), as well as drugs other than ACE inhibitors.

[1] The SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure, N. Engl. J. Med. *325(5)*:293-302, August 1, 1991.

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VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

For a Brief Summary of Prescribing Information, please see the following page.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASOTEC should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

VASOTEC® (ENALAPRIL MALEATE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASOTEC should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Contraindications: VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASOTEC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASOTEC should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats) and 50 times (in rabbits) the maximum recommended human dose.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients: Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC® (Enalapril Maleate) is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Pregnancy: Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Body As A Whole: Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*).

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia, impotence.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings: Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or congestive heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

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Cineradiography for Determination of Normal and Abnormal Function in Mechanical Heart Valves

Werner Vogel, MD, Hans Peter Stoll, MD, Wolfgang Bay, MD,
Gerd Fröhlig, MD, and Hermann Schieffer, MD

To determine the diagnostic value of cineradiography of mechanical heart valves, 112 cinefluoroscopic studies were performed in 76 patients with 95 valve prostheses (caged ball or disk valves, tilting disk and bileaflet valves). A patient group (n = 45) presenting with clinical or echocardiographic findings suggestive of valve-related complications was compared with a control group (n = 31) without such symptoms. Disk-opening angles (mean ± SD) for Medtronic Hall aortic valves were found to be significantly smaller (62.8 ± 11.1°) in patients than in control subjects (73.9 ± 1.6°; $p < 0.05$). Tissue ingrowth or thrombus formation, or both, demonstrated in 3 patients on subsequent reoperation, are considered as the main cause of incomplete or asymmetric disk opening. Opening and closing times did not differ significantly between patients and control subjects. Besides abnormal valve motion, structural defects such as strut fracture or leaflet escape could be rapidly detected by cineradiography if x-ray projections according to the particular valve design were used. Together with quantitative Doppler echocardiographic and clinical data, this method can help to give specific answers if the question is to either confirm or exclude imminent or acute valve malfunction. Thus, modern cineradiography is a highly valuable noninvasive diagnostic tool for both rapid management of emergency cases and routine follow-up of patients with mechanical heart valves.

(Am J Cardiol 1993;71:225–232)

Fluoroscopy has been widely used for identifying artificial heart valves[1,2] and detecting valve malfunction and valve-related complications, which were relatively frequent in the early years of valve surgery.[3–5] Meanwhile, patients with modern artificial valves are usually followed up by 2-dimensional and Doppler echocardiography. However, these techniques, although giving excellent insight into hemodynamics, do not allow a structural analysis of mechanical valves. Thus, they remain indirect methods where a mechanical problem is in question.

Although the visibility of mechanical valves with modern radiologic equipment has become excellent, systematic cineradiographic studies have been reported only for the functional analysis of single valve types (e.g., Björk-Shiley[6–9] or St. Jude[10,11] valves), for monitoring fibrinolytic therapy in acute valve thrombosis,[6,12] and for evaluating periprosthetic regurgitation.[13] The aim of the present study was (1) to establish normal values for opening and closing times of different types of current mechanical valves in vivo, (2) to compare opening and closing angles of tilting disk valves with the manufacturer's specifications, and (3) to show abnormalities in clinically suspected or surgically proven malfunction as will be demonstrated in individual cases.

Patient population and valve types: A total of 112 cineradiographic studies were performed in 95 mechanical heart valve substitutes that had been implanted in the aortic (n = 47), mitral (n = 46), and tricuspid (n = 2) positions in 76 patients. Fifty-nine patients had undergone single-valve replacement (33 aortic, 26 mitral), and 17 double-valve replacement (aortic and mitral in 15, aortic and tricuspid in 2) 70 ± 65 months (range 1 to 230) before the study. In 45 patients (patient group), we considered an indication for fluoroscopy because of clinical or Doppler echocardiographic[14] findings suggestive of valve-related complications (5 were emergency cases of pulmonary edema or cardiogenic shock, or both). Indications are listed in detail in Table I. In the remaining 31 subjects (control group) fluoroscopy was performed for different reasons: Older models of caged ball or tilting disk valves known to bear an increased risk of strut fracture or leaflet escape were screened for exclusion of early signs of such mechanical failure (e.g., Björk-Shiley valves before the monostrut era,[15–18] duromedics bileaflet valves[19]). Other subjects were examined in order to exclude valve thrombosis, e.g., if anticoagulation had been discontinued for noncardiac surgery. No control subject had clinical or Doppler echocardiographic signs of valve or cardiac dysfunction at the time of analysis.

From the Medizinische Universitätsklinik und Poliklinik, Innere Medizin III (Kardiologie), Homburg/Saar, Germany. Manuscript received February 11, 1992. Revised manuscript received and accepted August 17, 1992.

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TABLE I Indications for Cineradiography (patient group)

Indication	No. of Pts.	%
Heart failure*	10	22.2
Changed clicks/murmurs	7	15.6
TIA/stroke, dizziness	7	15.6
Hemolysis	7	15.6
Anticoagulation, irregular	5	11.1
Doppler gradient high†	4	8.9
Malfunction follow-up‡	3	6.6
Infective endocarditis	2	4.4
Total	45	100.0

*Heart failure unexplained by poor ventricular function or arrhythmias, or both.
†Gradient exceeding 30 mm Hg in aortic valve and 4 mm Hg in mitral/tricuspid valves.
‡Minor mechanical dysfunction without clear indication for reoperation.
TIA = transient ischemic attack.

TABLE II Distribution of Prosthetic Valves with Respect to Type, Site, and Relation to Patient or Control Groups

Valve Type	Aortic (pt./control)	Mitral (pt./control)	All (pt./control)
Starr-Edwards	4 (2/2)	2 (1/1)	7* (4/3)
Cooley-Cutter	1 (1/−)	− (−/−)	1 (1/−)
Björk-Shiley	14 (11/3)	4 (2/2)	18 (13/5)
Lillehei-Kaster	2 (1/1)	− (−/−)	2 (1/1)
Medtronic-Hall	36 (19/17)	1 (−/1)	37 (19/18)
St. Jude Medical	3 (1/2)	30 (20/10)	34* (22/12)
Duromedics	2 (−/2)	11 (1/10)	13 (1/12)
Total	62 (36/26)	48 (25/23)	112* (63/49)

*Include 2 tricuspid valves in the patient group.

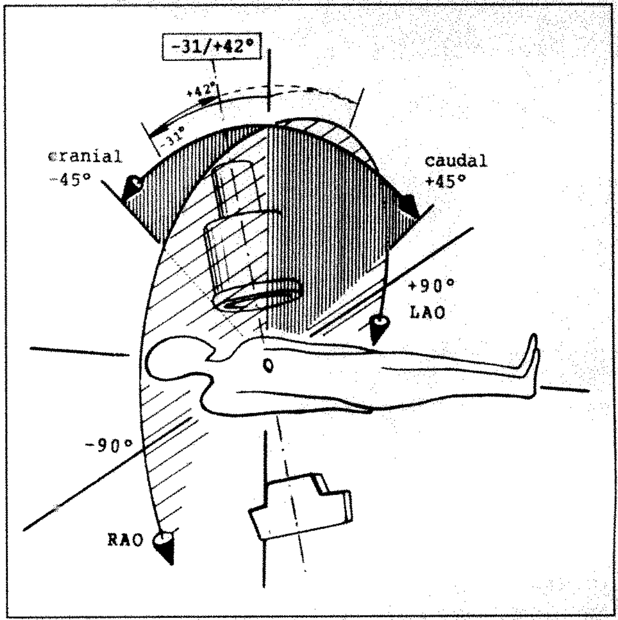


FIGURE 1. Range of craniocaudal skew *(vertical hatching)* and rotation *(horizontal hatching)* of x-ray tube for the identification of projections in valve cineradiography (see text). LAO/RAO = left/right anterior oblique view.

Numbers and types of investigated valves are listed in Table II. In all, 12 different models from 7 types of mechanical valves were examined. Most of the valves in the patient group could be matched with control valves of the same type.

METHODS

Fluoroscopy and cineradiography were performed in the supine patient with a monoplane x-ray system (Philips Poly Diagnost C) with digital imaging (Philips DCI-S Release 2.3). This system allows the position of the roentgen tube to be varied within a wide range of cranial to caudal skew (from −45 to +45°) and of right to left oblique rotation (from −120 to +120°), each projection being characterized by 2 (positive or negative) figures. For example, in a −31°/+42° projection the tube is tilted to a 31° cranial and rotated to a 42° left anterior oblique position (Figure 1). All valves were assessed as follows:

1. A sagittal (0°/0°) projection was taken for the identification of the valve and its steric orientation in situ.
2. The tube was then moved to a position with x-rays parallel to the valve ring plane. This allowed one to directly determine the occluder's excursions in caged

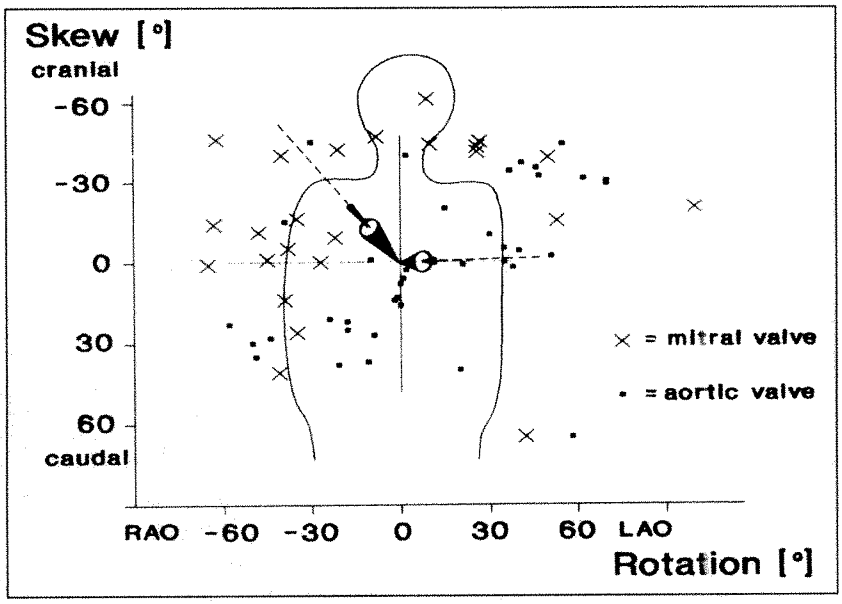


FIGURE 2. Projection angles of pivot views. Note the wide distribution of coordinates in individual valves. Mean values for all measurable mitral *(long arrow)* and aortic valves *(short arrow)* are shown. LAO/RAO = left/right anterior oblique view.

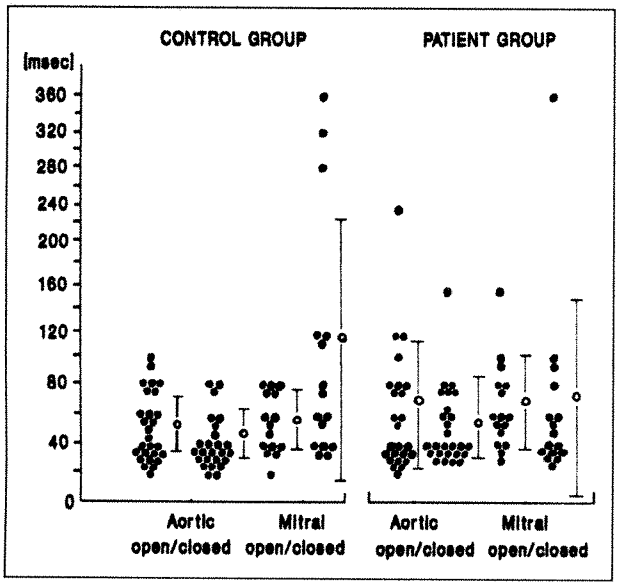


FIGURE 3. Opening and closing times (in milliseconds) of different types of mechanical valves. Differences between patients and control subjects are not significant.

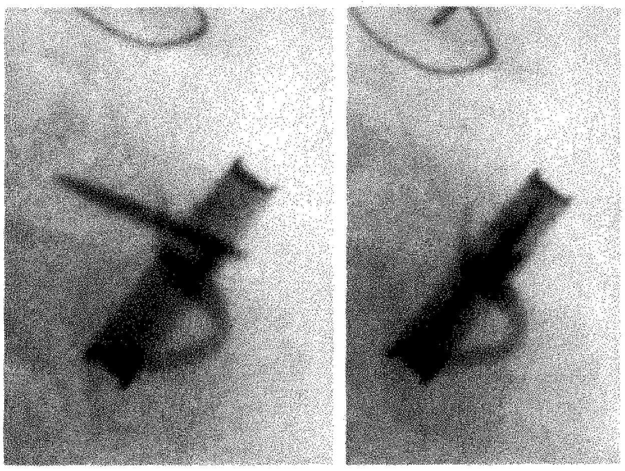


FIGURE 4. Normal opening (75°) and closing angle (0°) of a Medtronic-Hall aortic valve. Superimposed pivot supports indicate that the pivot view is correctly installed.

valves. In tilting valves, however, a "pivot" view (technically equivalent to the sectional elevation) with x-rays strictly parallel to the tilting axis had to be achieved in order to measure correctly opening and closing angles.

3. Additional projections were performed if any irregularities of disk motion were observed or a pivot view could not be obtained: a "disk" view with the beams parallel to the disk plane at full opening but perpendicular to the tilting axis. This view allows calculation of the opening angle with sufficient accuracy[6] and checking for correct seating of the occluder on its support. Special views were added to examine the welding points of struts in Björk-Shiley and caged valves.

4. The projection angles of each view were documented, and video prints and short cinefilm runs (3 to 6 heart cycles) were obtained for the subsequent functional analysis:

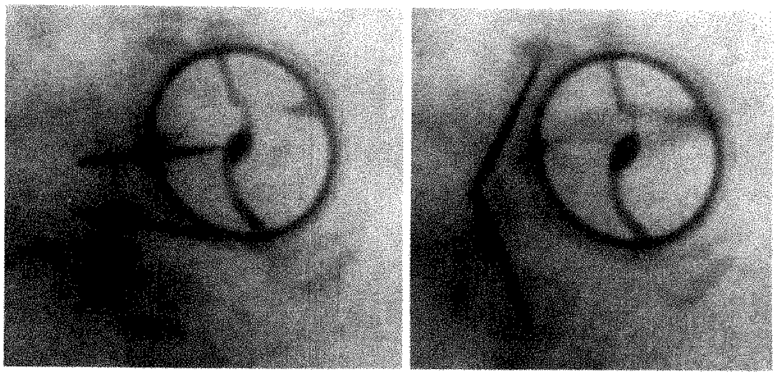
Valve motion was analyzed by measuring opening and closing angles from the pivot view and by evaluating the occluder's opening and closing speed using the shutter speed of 50 frames/s as a time marker. For example, if opening started in frame 1 and was being completed in frame 3, opening time was calculated to be 60 ms (with the exact opening time ranging between 40 and 60 ms). Accordingly, closing time, systolic and diastolic intervals and heart cycle length were measured. Differences between valve motion parameters of the patient and control group were statistically analyzed by use of the Mann-Whitney U test.

RESULTS

Valve orientation: In the group with 46 aortic tilting disk valves, a pivot view was not obtained in 4 patients (8.7%) for anatomic or technical reasons (invisible delrin disk of an early Björk-Shiley model in 1 patient). In the mitral group, 10 of 36 valves (27.8%) could not be viewed exactly along the pivot axis. Figure 2 shows the wide distribution of projection angles for the pivot views of tilting disk or bileaflet valves in the aortic and mitral position, respectively. The wide range is due to anatomic variations as well as the surgeon's choice for valve orientation and forces the radiographer to find individual projections for the specific views of each valve.

Valve motion—opening and closing speed: Normal disk or ball motion in different valve types was studied in 31 subjects in the control group with 48 valves. Irrespective of the valve size and heart cycle length, opening time was completed within 60 ms in >80% of all aortic valves. Only 2 aortic valves (1 Starr-Edwards, 1 Medtronic-Hall) required 80 to 100 ms for full opening. Opening and closing times in the patient group did not differ significantly from those in control subjects, with mean values and ranges being slightly higher in

FIGURE 5. Normal opening (10°, *left*) and closing angle (130°) of a 29 mm St. Jude Medical mitral valve seen from its pivot view. For complete analysis of this case a pivot view of the superimposed Medtronic-Hall aortic valve needs to be obtained by a further left rotation and cranial skew of the x-ray tube.



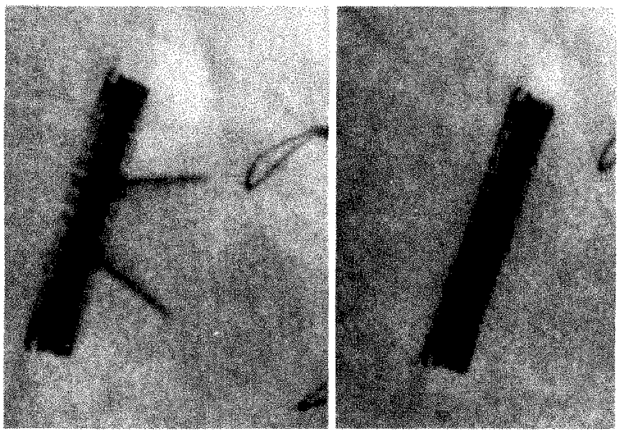


FIGURE 6. Normal opening and closing of a Duromedics mitral valve.

both aortic and mitral valves (Figure 3). Mitral opening time in both groups rarely exceeded 80 ms (100 ms in 2 and 160 ms in 1 patient with a periprosthetic leak; all had bileaflet valves without any mechanical malfunction).

Complete closing required up to 360 ms in some of the bileaflet mitral valves. This finding was infrequent and mostly due to an asymmetric closing in patients

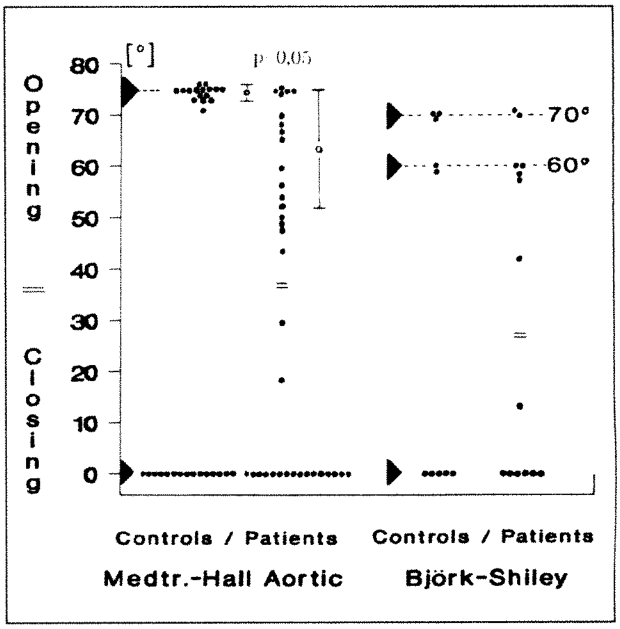


FIGURE 7. Opening and closing angles of tilting disk valves. *Black triangles and dotted lines* mark the specified opening angles of 75° in the Medtronic (Medtr.)-Hall aortic valve, and of 60 or 70° in Björk-Shiley valves, respectively. Note the wide range of abnormal angles in the patient group.

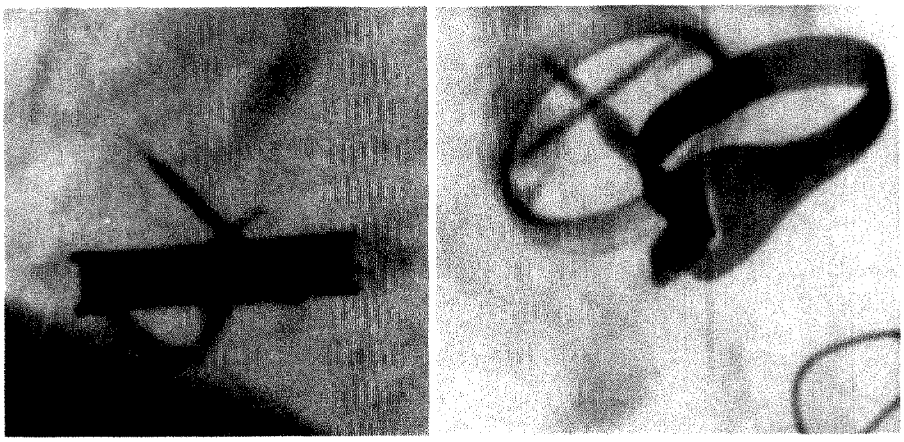


FIGURE 8. Pivot and disk view of Medtronic-Hall aortic valve with constantly asymmetric opening by only 50°. Patient had syncope 1 year after operation. Reoperation was refused because of advanced age and severe sternal and general osteoporosis. No change at cineradiography 1 and 2 years later; patient remained asymptomatic.

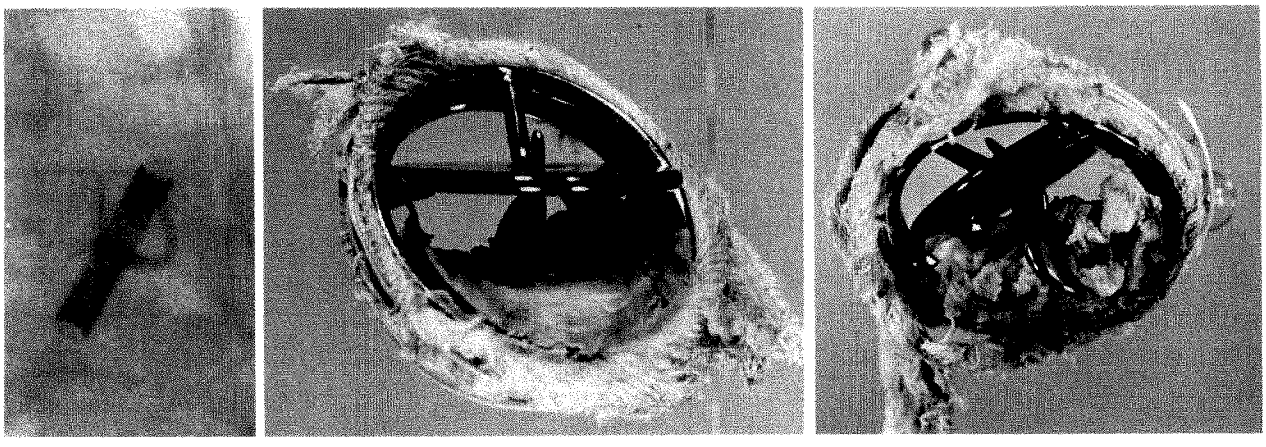


FIGURE 9. Reduced opening (44°, *left*) and closing (29°) with a Doppler gradient of 58 mm Hg and regurgitation at the Medtronic-Hall prosthesis 5 years after aortic valve replacement, and 2 years after change from warfarin to aspirin because of alopecia. Explanted valve shows asymmetric disk opening due to thrombus formation in the large segment of the valve orifice seen from the outflow *(center)* and inflow side *(right)*.

with atrial fibrillation. In none of the cases was it associated with clinically significant mitral regurgitation.

Valve motion—opening and closing angles: To compare disk excursions with the manufacturers' specifications, opening and closing angles were measured in all tilting disk and bileaflet valves in which a pivot projection had been achieved. Tilting disk valves close at 0°, with the disk forming a parallel radioopaque line within the valve ring (Figure 4). The only exception is the Lillehei-Kaster valve which closes at 18° and opens to a maximum of 80°. The Medtronic-Hall valves open to 75° (Figure 4) or 70° for the aortic and mitral models, respectively. Björk-Shiley disks open to 60 or 70° depending on the type. In St. Jude valves both leaflets form an angle of 120° (size ≤25 mm) or 130° (size ≥27 mm) when closed and 10° at full opening (Figure 5). Duromedics leaflets cover an angle of 38 and 28° for the open mitral and aortic valves, respectively; these angles, however, are particularly difficult to assess because of the curved shape of the leaflet and their poor visibility in the closed position (Figure 6).

Statistical analysis revealed that opening angles of Medtronic-Hall aortic valves were significantly smaller in patients (62.8 ± 11.1°, range 44 to 75°) than in control subjects (73.9 ± 1.6°, range 71 to 76°). Opening angles >70° were found in only 5 cases in the patient group. These had been investigated for reasons not highly suggestive of mechanical failure, namely hemolysis, bleeding complication, unexplained syncope, and infective endocarditis (2 cases). In the remaining valves (70%), opening angles were ≤69°. In Björk-Shiley valves, opening angles met the specified values of 60 or 70° with a deviation of ≤3° except the case described later. Closing (0°) was normal in all but 3 patients (1

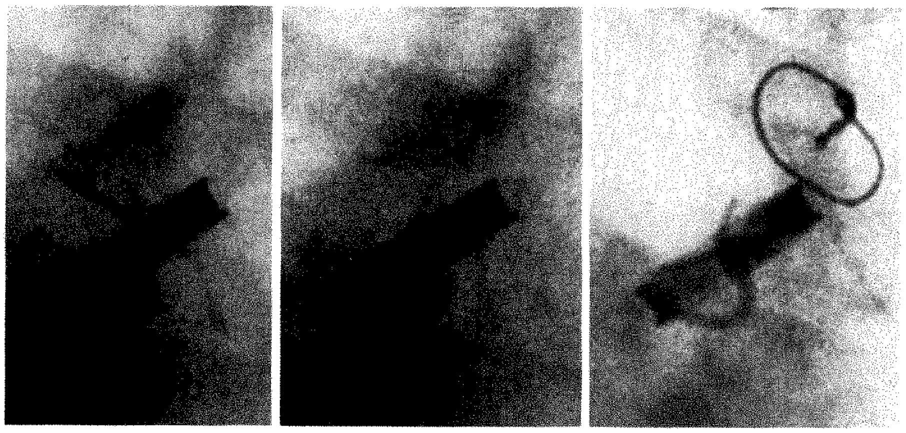


FIGURE 10. Reduced opening angle (68°) of a Medtronic-Hall aortic valve in an asymptomatic patient; Doppler gradient was 60 mm Hg. At follow-up after 4 weeks, closing deficit (18°) with aortic regurgitation and dyspnea developed despite correct anticoagulation. Intraoperatively a pannus at the inflow (large segment) and a fresh thrombus at the outflow side (small segment) were detected and removed. Follow-up after 1 year again showed an opening angle of 68°, with a Doppler gradient of 25 mm Hg.

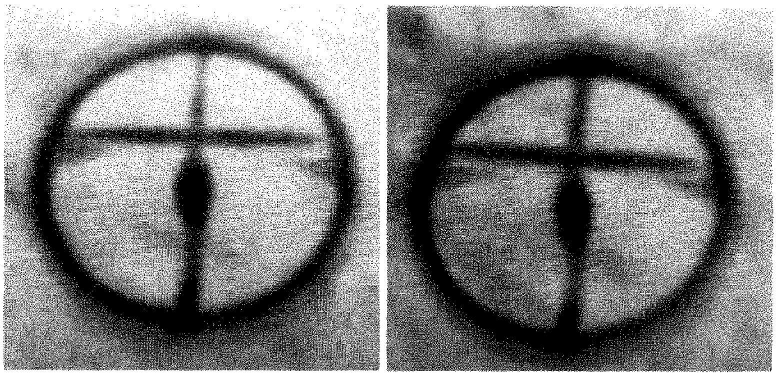


FIGURE 11. Intermittent slight asymmetry *(left)* of aortic valve opening in a patient with low left ventricular output. Normal disk view *(right)* during a postextrasystolic contraction in the same patient.

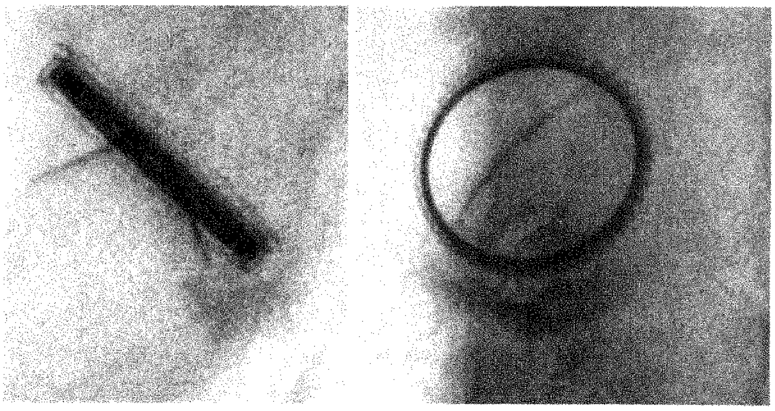


FIGURE 12. Immobilization of the caudal leaflet of a 31 mm Duromedics mitral valve 1 year after implantation by massive calcification of the mitral ring (see text).

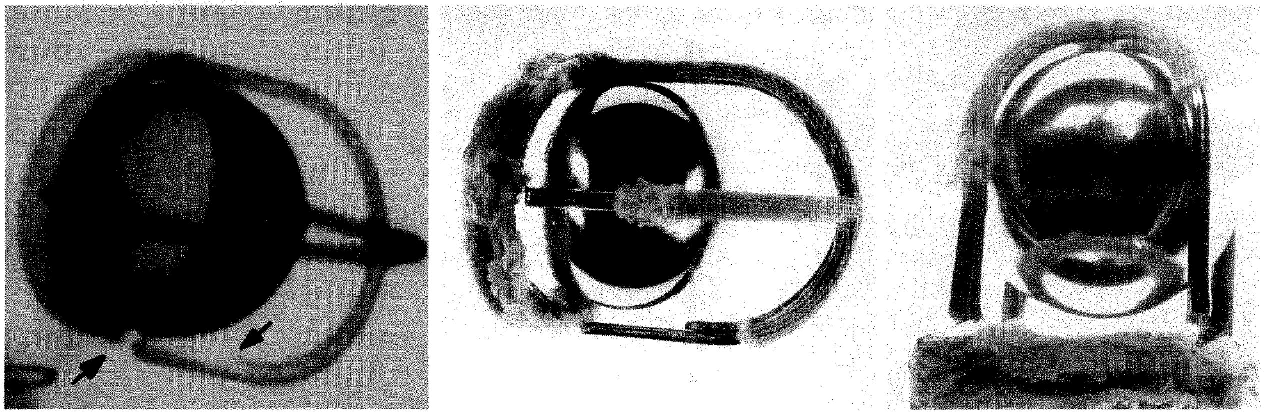


FIGURE 13. Starr-Edwards model 6400 mitral valve 4 years after implantation. Strut fracture at the base ring and escape of a 12 mm fragment of the inner track were detected by cineradiography *(arrows)*. Explanted valve even showed 2 broken welding points and marked cloth injury.

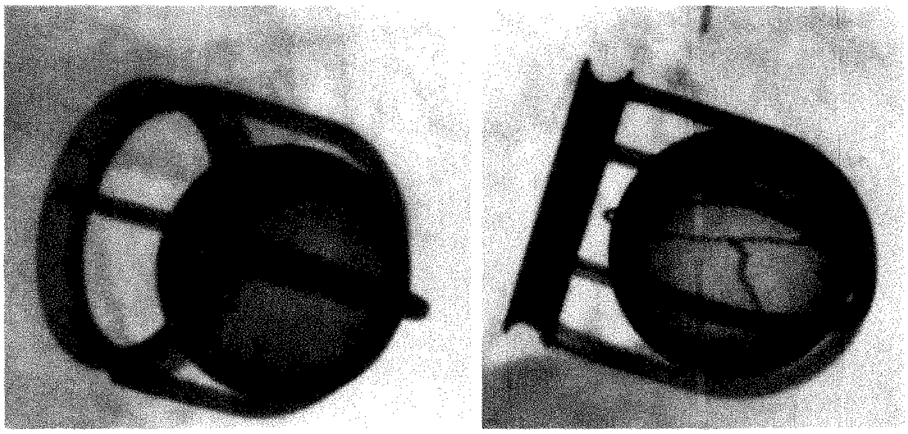


FIGURE 14. Starr-Edwards model 6400 mitral valve 16 years postoperatively at full opening. Intact welding points at the base ring but widened cage with 1 mm distance between upper strut and ball are seen with visible and audible (diastolic rattling) lateral play of the ball (see text).

with a Björk-Shiley and 2 with Medtronic-Hall aortic valves) with subsequently confirmed valve thrombosis (Figure 7). Opening and closing angles of all St. Jude Medical valves were again close (within 3°) to specified values (opening angles, 10 to 13°, closing angles, 120 to 122° or 130 to 133°).

A frequent observation in valves with reduced opening angles was a constant asymmetry of the disk at maximal opening in the disk view (Figure 8). As a cause of this functional abnormality, tissue ingrowth or thrombus formation, or both, between the disk and the supporting pivot were suspected and could be confirmed in 3 patients who subsequently underwent reoperation. For example, in the case demonstrated in Figure 9, opening and closing angles of 44 and 29°, respectively, were caused by a thrombus extending from 1 pivotal support to the major segment of the valve orifice with severe impairment of disk mobility. Similarly, an upstream pannus formation alongside the small segment of a Björk-Shiley spherical disk valve with a fresh thrombus around the outlet strut were suggested from cineradiographic data (opening and closing angles 42 and 13°, opening and closing speed 240 and 160 ms, respectively) and confirmed during emergency surgery. Another case with a combination of pannus and fresh thrombus formation could be detected cineradiographically (Figure 10).

Incomplete valve opening could also be observed in patients with low cardiac output or arrhythmias. Disk-pivot contact in these cases, however, changed during several heart cycles and appeared to be normal in single (e.g., postextrasystolic) contractions (Figure 11).

In 1 case of mitral valve replacement with a 31 mm Duromedics valve, the inferoposterior leaflet was stuck in severely calcified tissue in an almost closed position (Figure 12). This mass had already been present at the time of implantation, and had only partly been resected

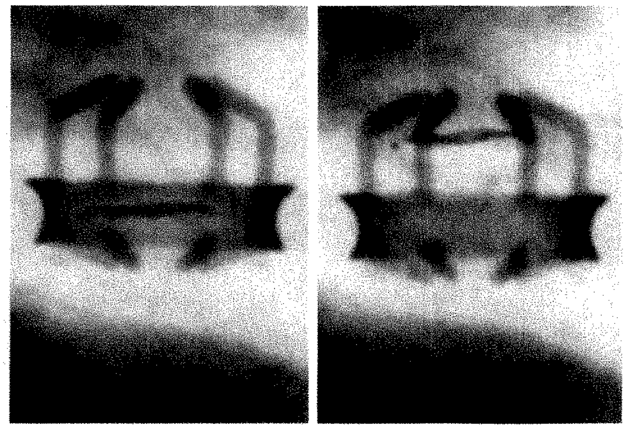


FIGURE 15. Cooley-Cutter caged disk aortic valve 15 years after implantation, with normal movement of an opacified biconical disk (calcified infiltration?). Valve exchange was necessary because of aortic regurgitation due to subvalvular pannus formation and intermittent "cocking" of the disk.

because of its infiltration into the posterior left ventricular wall. One year postoperatively, after a perfect reconvalescence, the patient again developed slight dyspnea on exertion. Doppler echocardiography revealed a small valve area of 1.6 cm^2 (measured by the pressure half-time method), and a relatively high gradient of 4 to 6 mm Hg with respect to the large valve size.[14]

Structural defects: A strut fracture in a Starr-Edwards mitral valve (model 6400) 4 years after implantation could be detected by cineradiography. A 12 mm fragment of the inner metal track appeared to be broken and embolized into the left ventricle; the welding point was fractured at the base ring. The valve was removed because total break of the cage was imminent. The situation then turned out to be even more serious because the excised valve showed that 2 of the 4 struts had already broken at the metal ring base (Figure 13). In another case of the same valve type, the aspect of the welding points appeared normal (Figure 14), but marked "lateral" excursions of the ball were suggestive of cage wear as will be discussed next.

One patient had an opaque layer in the "equatorial" plane of the biconical disk in an aortic Cooley-Cutter valve, which had to be exchanged after 15 years of uneventful functioning because of aortic regurgitation and a subvalvular pannus formation with intermittent "cocking" of the disk, demonstrated intraoperatively. During cinefluoroscopy, disk movement itself appeared normal (Figure 15).

Two of our patients with cardiogenic shock presented with an outlet strut fracture of a Björk-Shiley convexoconcave valve. Immediately after admission diagnosis was cineradiographically confirmed in both patients. The first case was a 37 year-old man who had had an uncomplicated aortic valve replacement 8 years before admission. He was seen in cardiogenic shock 4 hours after the onset of severe dyspnea, and died from low ventricular output despite immediate reoperation. The other patient was a 55 year-old man who had been followed 7 years after Björk-Shiley mitral valve replacement without complications. He was referred to our hospital 7 hours after the onset of acute heart failure which had been refractory to usual therapy. Leaflet escape had not been suspected clinically because closing clicks were clearly audible on auscultation. Changing loudness of the clicks had been attributed to the preexisting absolute arrhythmia. This misleading constellation could later be explained by a concomitant mild aortic stenosis that entrapped the large disk within the left ventricle and allowed it to be thrown on the metal valve ring every 2 to 3 systoles. The patient was protected from massive pulmonary edema for several hours by this "intermittent" mitral competence. Unfortunately, he also died in refractory left ventricular failure on the seventh day after emergency reoperation.

DISCUSSION

From our data we can state that cineradiography provides clear information on structure and function of most mechanical heart valve prostheses. In roughly 85% of all tilting disk valves disk opening and closing angles can be directly measured and compared with the manufacturer's specifications, since a correct pivot view reproduces the designer's sectional elevation. In the remaining valves, the opening angle can be obtained from the disk view by simple calculation. The excellent visibility of the disk in a profile view with modern x-ray systems makes the direct method applicable for virtually all current disk valves. It is clearly superior to indirect methods[6–8] that are dependent on optimal imaging and cannot always rule out minimal closing deficits. Our findings in the control group are consistent with published reports.[8,9,10,12] They suggest that a normal disk opening can be assumed if the measured opening angle meets the designated value within a small deviation of up to 3 to 4° depending on image quality, which may be poor in obese patients. As a consequence, an opening deficit of ≥5° should aid in further clarifying whether there is an anatomic (pannus, thrombus) or a functional reason (arrhythmia, low output, valve orientation). Extensive calcification of the valve ring may be indicative of tissue ingrowth to the valve orifice that has been previously shown to be a common problem after valve replacement,[20] especially in patients with incorrect anticoagulation.[4] According to the results of other investigators,[9,12] the opening or closing times of normal artificial valves rarely exceed 80 ms; the exception is the bileaflet valve in the mitral position, especially in patients with

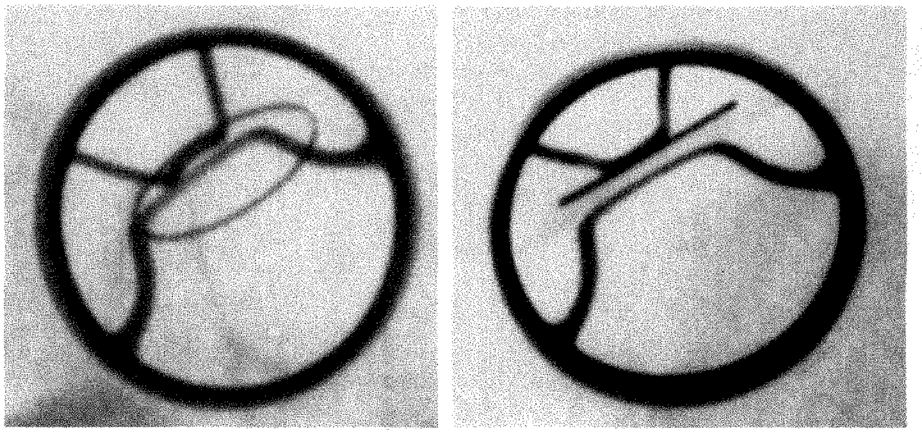


FIGURE 16. Björk-Shiley 70° convexo-concave mitral valve 8 years after implantation. Note the slight asymmetry of the outlet strut and disk at full opening. 1 year later the situation was identical in the orifice *(left)* and disk *(right)* views.

atrial fibrillation who may intermittently have a marked delay of one leaflet's closing movement, usually without serious hemodynamic consequences. Severe and constant impairment of disk mobility in terms of low opening or closing speed is suggestive of acute thrombotic obstruction, but obviously it is not a sensitive sign. In our 3 patients with acute aortic valve thrombosis, both opening and closing times were abnormal in only 1; the others had prolonged opening or completely normal values (all within the reduced excursion angles).

Structural defects in caged valves were mostly related to ball variance or strut cloth injury, and rarely to a real damage to the cage itself[21] as in our patient (Figure 13). It is not clear whether such a break is facilitated by the long-term wear of the struts due to lateral excursions of the metal ball. Such "oscillations" perpendicular to the normal motion axis were clearly visible and audible as a rattling diastolic noise on auscultation in the case presented in Figure 14.

Severe structural defects have been reported for many mechanical prostheses.[19,22] The strut fracture problem of Björk-Shiley valves continues to be a challenge in the management of patients involved.[15–18,23,24] Whether serial follow-up of such patients by cineradiography could identify patients at risk (e.g., by detection of slight strut deformation [Figure 16], or by identifying other possible predictors of fracture) needs to be established. In our institution, we therefore plan a screening program of all pre-monostrut Björk-Shiley valves with the described cineradiographic method.

The patient's only risk with cineradiography is x-ray exposure with fluoroscopy times of 5 to 10 minutes (which can be reduced to about one third in reexaminations if projection angles are known) and cinefilm exposure times between 20 and 60 seconds. The small hazard seems greatly outweighed by the diagnostic benefit of this noninvasive method.

Interactions between biologic structures and a technical device over a lifetime are not predictable because they are dependent on several factors, namely the underlying disease, valve type and size. This has been emphasized many years ago.[5,23] Technical devices need precise survey, and this applies especially to artificial heart valves because they constantly interfere with living tissue. Advantage can be taken of modern technical equipment to get a closer look at this complex interrelation. Magnetic resonance imaging may be a promising technique for special questions, but is still of limited value for studying mechanical valves.[25] Doppler echocardiography is a clear advance for hemodynamic follow-up after valve replacement. Cineradiography with its immediate and high-resolution documentation capabilities provides unique information unavailable from other techniques, especially if early postoperative data can be compared with those from later follow-up. Therefore, this simple method should be routinely used for patients with artificial heart valves.

REFERENCES

1. Mehlmann DJ, Resnekov L. A guide to the radiographic identification of prosthetic heart valves. *Circulation* 1978;57:613–623.

2. Mehlmann DJ. A guide to the radiographic identification of prosthetic heart valves: an addendum. *Circulation* 1984;69:102–105.

3. Starr A, Grunkemeier GL, Lambert LE, Thomas DR, Sugimura S, Lefrank EA. Aortic valve replacement: a ten-year follow-up of non-cloth-covered caged ball prostheses. *Circulation* 1977;56:II:II-133–II-139.

4. Smithwick W, Kouchoukos NT, Karp RP, Pacifico AD, Kirklin JW. Late stenosis of Starr-Edwards cloth-covered prostheses. *Ann Thorac Surg* 1975;20:249–254.

5. Roberts WC. Choosing a substitute cardiac valve: type, size, surgeon. *Am J Cardiol* 1976;38:633–644.

6. Venkataraman K, Beer RF, Mathews NP, Carl JR, Harrison EC, Turner AF, Finck EJ. Thrombosis of Björk-Shiley aortic valve prostheses. Report of 3 cases and a method of cineradiographic assessment of the opening angle. *Radiology* 1980;137:44–47.

7. Ishimaru S, Furuawka K, Takahashi M. Cineradiographic evaluation of the convexo-concave Björk-Shiley prosthetic valve in mitral position. *Scand J Thorac Cardiovasc Surg* 1983;17:211–215.

8. Cousin AJ, Soto B. New cineradiographic methods for assessment of Bjork- Shiley valve integrity. AJR *Am J Roentgenol* 1986;147:1139–1144.

9. Albrechtsson UG, Thulin LI, Olin CL. Cineradiographic functional evaluation of the Björk-Shiley monostrut prosthesis. A follow-up study of 46 consecutive patients. *Scand J Thorac Cardiovasc Surg* 1987;21:91–95.

10. Castaneda-Zuninga W, Nicoloff D, Jorgensen C, Nath PH, Zollikofer C, Amplatz K. In vivo radiographic appearance of the St. Jude valve prosthesis. *Radiology* 1980;134:775–776.

11. Hartz RS, LoCicero J, Kucich V, DeBoer A, O'Mara S, Meyers SN, Michaelis LL. Comparative study of warfarin versus antiplatelet therapy in patients with a St. Jude Medical valve in the aortic position. *J Thorac Cardiovasc Surg* 1986;92:684–690.

12. Czer LS, Weiss M, Bateman TM, Pfaff JM, DeRobertis M, Eigler N, Vas R, Matloff JM, Gray RJ. Fibrinolytic therapy of St. Jude valve thrombosis under guidance of digital cinefluoroscopy. *J Am Coll Cardiol* 1985;5:1244–1249.

13. Green CE, Glass-Royal M, Bream PR, Soto B, Elliott LP. Cinefluoroscopic evaluation of periprosthetic cardiac valve regurgitation. *Am J Roentgenol* 1988;151:455–459.

14. Burckhardt D, Hoffmann A, Amann FW, Grädel E. Noninvasive assessment of pressure gradients across prosthetic heart valves by doppler ultrasound. In: DeBakey ME, ed. Advances in Cardiac Valves. London: Yorke Medical Books, 1983:199–205.

15. Lindblom D, Björk VO, Semb BKH. Mechanical failure of the Björk-Shiley valve. Incidence, clinical presentation, and management. *J Thorac Cardiovasc Surg* 1986;92:894–907.

16. Ostermeyer J, Horstkotte D, Bennet J, Huysmans H, Lindblom D, Olin C, Semb G. The Björk-Shiley 70° convexo-concave prosthesis strut fracture problem (present state of information) *Thorac Cardiovasc Surg* 1987;35:71–77.

17. Hiratzka LF, Kouchoukos NT, Grunkemeier GL, Miller DC, Scully HE, Wechsler AS. Outlet strut fracture of the Björk-Shiley 60° convexo-concave valve: current information and recommendations for patient care. *J Am Coll Cardiol* 1988;11:1130–1137.

18. Lindblom D, Rodriguez L, Björk VO. Mechanical failure of the Björk-Shiley valve. Updated follow-up and considerations on prophylactic rereplacement. *J Thorac Cardiovasc Surg* 1989;97:95–97.

19. Moritz A, Klepetko W, Khünl-Brady G, Schreiner W, Pabinger I, Bailer H, Lang I, Wolner E. Four year follow-up of the Duromedics Edwards bileaflet valve prostheses. *J Cardiovasc Surg* 1990;31:274–282.

20. Yoganathan AP, Corcoran WH, Harrison EC, Carl JR. The Björk-Shiley aortic prosthesis: flow characteristics, thrombus formation and tissue overgrowth. *Circulation* 1978;58:70–76.

21. Zumbro GL, Cundey PE, Fishback ME, Galloway RF. Strut fracture in DeBakey valve. Successful reoperation and valve replacement. *J Thorac Cardiovasc Surg* 1977;73:469–470.

22. Orsinelli DA, Becker RC, Cuénoud HF, Moran JM. Mechanical failure of a St. Jude Medical Prosthesis. *Am J Cardiol* 1991;67:906–908.

23. Taylor K. Acute failure of artificial heart valves. The risk is small. *Br Med J* 1988;297:996–997.

24. Treasure T. Management of patients with Björk-Shiley prosthetic valves. *Br Heart J* 1991;66:333–334.

25. Randall PA, Kohmann LJ, Scalzetti EM, Szeverenyi NM, Panicek DM. Magnetic resonance imaging of prosthetic cardiac valves in vitro and in vivo. *Am J Cardiol* 1988;62:973–976.

Balloon Mitral Commissurotomy in Patients Aged ≥70 Years

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Of 280 patients treated by balloon mitral commissurotomy (BMC) between 1987 and 1991, 28 (10%) were ≥70 years old. Two patients with associated significant aortic stenosis were excluded from the study. Older patients more often were in New York Heart Association class III or IV (84 vs 67%; $p < 0.007$) and atrial fibrillation (61 vs 36%; $p < 0.0001$), and had a higher echocardiographic score (9.3 ± 2 vs 8 ± 1.6; $p < 0.0004$) and a lower baseline cardiac index (2.1 ± 0.6 vs 2.4 ± 0.6 liters/min/m^2; $p < 0.03$) than younger ones. Baseline mean pulmonary pressure (37 ± 11 vs 34 ± 12 mm Hg), transmitral gradient (14 ± 4 vs 14 ± 5 mm Hg) and valve area (1.0 ± 0.4 vs 1.1 ± 0.3 cm^2) were not different between older and younger patients (p = NS). Acute complications during the procedure (including cardiac perforation, embolism, severe mitral regurgitation and surgical atrial shunt), and 30-day mortality after BMC were more frequent in older than younger patients (27 vs 9% [$p < 0.01$], and 12 vs 0.8% [$p < 0.005$], respectively). A complete success, defined as a mitral valve area increase >25% and postmitral valve area >1.5 cm^2 was obtained in 16 of the 22 older patients (72%) with the completed procedure (compared with 81% of younger ones; $p = 0.1$). At 6 months, 20 of the 21 surviving patients (95%) who had not crossed over to surgery had an improvement of ≥1 functional class, and 13% remained improved after a mean follow-up of 28 ± 17 months. Long-term survival of older patients was compared with that of our first 96 younger ones dilated before 1990. The total survival rate at 3 years was 70% in older patients and 92% in younger ones ($p < 0.001$). Thus, BMC can be an effective therapy for pa-tients aged ≥70 years, but has an increased risk of morbidity and mortality compared with in younger ones. However, the hemodynamic success rate in patients aged ≥70 years with the completed procedure, and the long-term cardiac survival in those with a good initial result are similar to those in younger ones. Therefore, BMC can be performed in older patients with an acceptable risk compared with that of medical treatment or surgery.

(Am J Cardiol 1993;71:233–236)

Balloon mitral commissurotomy (BMC) was first described by Inoue et al[1] in 1984, and with increased experience and better patient selection, this technique is now recognized as an effective, alternative treatment to surgical commissurotomy for symptomatic mitral stenosis with favorable valve morphology.[2–4] The mechanism involved in the increase of the orifice area appeared to be commissural splitting fracture of calcified leaflets and partial valve disruption,[5,6] similar to closed surgical commissurotomy.[7,8] Both procedures have excellent results, with a low risk in patients with mobile, pliable, minimally thickened and only mildly calcified valves. BMC was originally proposed in certain centers as palliative treatment for elderly patients at high risk for surgery or for whom surgery is contraindicated.[9–12] Results appear to be less satisfactory in these patients who more frequently have immobile, thickened and calcified valves. However, immediate and long-term outcome have not been studied in a large series. This study describes the early and late outcome of patients aged ≥70 years who underwent BMC for symptomatic mitral stenosis and compares these results with those of younger patients.

METHODS

Study patients: Of 280 consecutive cases of BMC performed from March 1987 to December 1991 at the Montreal Heart Institute, 28 patients (10%) were aged ≥70 years (252 were aged <70 years). Two patients with associated significant aortic stenosis were excluded from the study. Clinical characteristics of the patients are listed in Table I. Associated valve diseases were mild aortic stenosis in 3, mild aortic regurgitation in 3, tricuspid stenosis in 1, and severe tricuspid regurgitation in 5.

Echocardiographic measurements: Echocardiographic data were obtained the day before, and between 24 and 48 hours after the procedure. Left atrial diameter was measured from the M-mode echocardiogram as previously described.[13] Morphologic characteristics of the mitral apparatus were evaluated according to the scoring system of Wilkins et al.[14] Baseline echocardiographic characteristics of the mitral valve are listed in Table II. The echocardiographic score and left atrial diameter were greater in patients aged ≥70 years, whereas mean transmitral gradient and mitral valve area were not different between the 2 groups.

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TABLE I Clinical Characteristics of 26 Patients Aged ≥70 Years and 252 Aged <70 Years

	≥ 70 Years (n = 26)	< 70 Years (n = 252)	p Value
Age (year)	74 ± 2	50 ± 11	0.0001
Women/men	18/8 (70/30%)	214/38 (85/15%)	0.07
Previous embolism	6 (23%)	35 (14%)	NS
Prior mitral commissurotomy	2 (7%)	55 (22%)	NS
Atrial fibrillation	16 (61%)	91 (36%)	0.0001
X-ray mitral calcium	13 (50%)	106 (42%)	NS
NYHA class III or IV	22 (84%)	169 (67%)	0.007
Coronary artery disease	5 (19%)	23 (9%)	NS
Associated valve diseases	7 (27%)	58 (23%)	NS

NYHA = New York Heart Association.

TABLE II Baseline Echocardiographic Characteristics of 26 Patients Aged ≥ 70 Years and 252 Aged < 70 Years

	≥70 Years (n = 26)	< 70 Years (n = 252)	p Value
Left atrial diameter (mm)	57 ± 8	49 ± 7	0.0001
Echocardiographic score	9.3 ± 2.0	8.0 ± 1.6	0.0004
Leaflet mobility	2.5 ± 0.5	2.2 ± 0.5	0.003
Leaflet thickness	2.3 ± 0.6	2.0 ± 0.4	0.004
Leaflet calcium	2.2 ± 0.9	1.7 ± 0.8	0.007
Subvalvular disease	2.3 ± 0.7	2.0 ± 0.6	0.01
Mitral valve gradient (mm Hg)	11 ± 4	10 ± 4	NS
Mitral valve area (cm^2)			
Planimetry	1.1 ± 0.4	1.1 ± 0.3	NS
Pressure half-time	1.0 ± 0.3	1.1 ± 0.6	NS
Mitral regurgitation[16]	1.0 ± 0.7	0.7 ± 0.6	0.06

TABLE III Hemodynamic Results Before and After Completed Balloon Mitral Commissurotomy in 22 Patients Aged ≥70 Years

	Before BMC	After BMC	p Value
Cardiac output (L/min)	3.2 ± 1.0	3.9 ± 1.2	0.004
Cardiac index (L/min/cm^2)	2.1 ± 0.6	2.5 ± 0.7	0.007
Pressure (mm Hg)			
LA–LV MDG	13.9 ± 4.6	6.9 ± 3.0	0.0001
Left atrial	23 ± 5	18 ± 6	0.001
V wave	35 ± 9	25 ± 13	0.01
Systolic pulmonary artery	58 ± 21	56 ± 18	NS
Mean pulmonary artery	37 ± 11	34 ± 10	0.1
Total pulmonary resistance (dynes · s^{-1}/cm^{-5})	1,066 ± 625	679 ± 340	0.0003
Mitral regurgitation[16]	0.9 ± 0.7	1.2 ± 0.9	0.001
Mitral valve area (cm^2)	1.0 ± 0.4	1.8 ± 0.7	0.0001

BMC = balloon mitral commissurotomy; LA–LV MDG = left atrial–ventricular mean diastolic gradient.

Cardiac catheterization and balloon mitral commissurotomy: Informed consent for the procedure and consultation in cardiac surgery were obtained for all patients. The procedure and hemodynamic measurements were previously described.[15] Mitral valve area was calculated with the Gorlin formula. Left ventriculography in the 30° right anterior oblique projection was performed in all patients before and after BMC. Mitral regurgitation was quantified according to the criteria of Sellers et al.[16] Baseline cardiac index was less (2.1 ± 0.6 vs 2.4 ± 0.6 liters/min/m^2; p <0.03) and total pulmonary resistance greater (1,066 ± 625 vs 766 ± 442 dynes • s^{-1} • cm^{-5}; p <0.001) in patients aged ≥70 years, whereas baseline mean pulmonary pressure (37 ± 11 vs 34 ± 12 mm Hg), mean transmitral gradient (14 ± 4 vs 14 ± 5 mm Hg) and valve area (1.0 ± 0.4 vs 1.1 ± 0.3 cm^2) were not different between the 2 groups (p = NS). BMC was performed by the transseptal anterograde technique. Procedure-related characteristics were identical between patients aged ≥ and <70 years, using 2-balloon or bifoil balloon catheters in 88 vs 95% (p = NS), with a ratio of effective balloon dilating area to body surface area of 4.0 ± 0.9 vs 3.9 ± 0.5 (p = NS) (number of inflations 4.0 ± 1.7 vs 4.1 ± 1.9 [p = NS], and duration of dilation 30 ± 16 vs 33 ± 27 seconds [p = NS]).

Complete success was defined as a final mitral area >1.5 cm^2 and an increase in mitral valve area >25%. An incomplete success was defined as a mitral valve area >1.0 but <1.5 cm^2, with an increase in mitral valve area >25%. Hemodynamic failure was defined as a final mitral valve area <1 cm^2 or an increase in mitral valve area <25%.

Follow-up: Long-term follow-up data were obtained prospectively during hospital visits at 3 and 6 months after the BMC, and yearly thereafter. Echocardiographic data were obtained on a routine basis at 6 months of follow-up and were limited to the occurrence or worsening of symptoms thereafter.

Statistical analysis: Continuous variables (expressed as mean ± SD) were compared with nonpaired or paired Student's *t* test when appropriate. Categoric variables were compared with the chi-square test with the Yates correction when appropriate. Multiple logistic regression analysis and stepwise logistic regression were performed in the standard manner. Survival curves were constructed using the Kaplan-Meier actuarial method, and comparisons between groups were obtained with the log-rank statistic. A p value <0.05 was considered significant.

RESULTS

Technical failures and complications: Acute complications during the procedure (including cardiac perforation, embolism, severe mitral regurgitation and surgical atrial shunt) (27 vs 9%; p <0.01), and 30-day mortality after BMC (12 vs 0.8%; p <0.005) were more frequent in patients aged ≥70 years. Two patients had technical failure; an 81-year-old with an enlarged atrium (70 mm) without acute complication, and a 79-year-old died 36 hours later because of multisystem failure. BMC could not be completed in 2 patients; a 73-year- old with left ventricular perforation died 24 hours after emergency surgery, and another 73-year-old with left atrial perforation and acute tamponade underwent emergency surgery without further complications.

Major complications occurred in 4 of 22 patients with the completed procedure; 2 (aged 80 and 81 years, respectively) had a severe confusional state after BMC without any sequelae, 1 had severe atrial shunting with a ratio of pulmonary to systemic flow of 2.2, and a 79-year-old died 48 hours after BMC due to a cerebral embolism.

Immediate hemodynamic results: Hemodynamic results before and after BMC in the 22 patients aged

$\geq$70 years with the completed procedure are listed in Table III. A complete success was obtained in 16 patients (72%), an incomplete success in 3 (14%), and hemodynamic failure in 3 (14%). Mean mitral valve area increase was 0.79 ± 0.54 cm^2. Results were slightly better in patients aged <70 years, with complete hemodynamic success obtained in 81%, incomplete success in 15%, hemodynamic failure in 4% ($p = 0.1$), and a mitral valve area increase of 0.94 ± 0.65 ($p = 0.2$). By univariate analysis, hemodynamic success in patients aged $\geq$70 years (vs failure or incomplete success) was correlated with a greater mitral valve area (1.1 ± 0.3 vs 0.6 ± 0.3 cm^2; $p < 0.001$) and higher cardiac output (3.5 ± 0.8 vs 2.5 ± 0.9 liter/min; $p < 0.01$), and a reduced total pulmonary resistance (816 ± 318 vs 1,538 ± 798 dynes • s^{-1} • cm^{-5}; $p < 0.002$), but not with a mean echocardiographic score (8.8 ± 1.9 vs 10.3 ± 1.7; $p = 0.08$). By stepwise logistic regression, mitral valve area ($p < 0.01$) and total pulmonary resistance ($p < 0.01$) were independent predictors of success.

Angiographic mitral regurgitation, graded on a scale of 0 to 4, increased after BMC in patients aged $\geq$70 years (0.9 ± 0.7 to 1.2 ± 0.9; $p < 0.009$). Mitral regurgitation remained unchanged after BMC in 14 of 22 patients (60%) with the completed procedure, and increased by 1 grade in 8 patients and by 2 grades in the remaining one. Only 1 patient had grade 3/4 mitral regurgitation after BMC. Uni- and multivariate analyses did not identify any predictor of mitral regurgitation increase. Mean baseline mitral regurgitation was less in patients aged <70 years (0.6 ± 0.6 vs 0.9 ± 0.7; $p < 0.01$), but mean mitral regurgitation increase was similar in both groups (0.3 ± 0.6 vs 0.3 ± 0.4; p = NS).

Atrial shunting was detected by venovenous dye-dilution curves immediately after BMC in 75% of patients aged $\geq$70 years (vs 71% in younger ones; p = NS). Only 3 patients (14%) had a ratio of pulmonary to systemic flow >1.5 (vs 9% in younger ones). Uni- and multivariate analyses did not identify any predictor of atrial shunting in older patients.

Long-term follow-up: Clinical follow-up was obtained in all patients aged $\geq$70 years, and extended to 28 ± 17 months. Death during follow-up occurred in 5 patients, including 3 noncardiac (neoplasia) and 2 cardiac deaths at 1 and 7 months in 2 patients with hemodynamic failure in whom surgery was contraindicated. Only 1 patient had crossed over to emergency surgery for left atrial perforation during BMC. At 6 months, 18 of the 21 surviving patients (86%) who had not crossed over to surgery were in class I or II, and 20 (95%) had an improvement of $\geq$1 functional class and 12 (57%) of 2 classes. In comparison with 6-month clinical status, functional class at the end of follow-up was unchanged in 13 patients and worsened by 1 grade in 4. Patients with a long-term functional improvement had a lower baseline echocardiographic score than did the remaining ones (7.8 ± 2.0 vs 10.6 ± 1.7; $p < 0.01$).

Six-month echocardiographic measurement of the mitral valve area by pressure half-time diagnosed restenosis (defined as a decrease of >50% of the gain achieved in mitral valve area and a mitral valve area <1.5 cm^2) in 2 of 16 patients who had complete hemodynamic success. These 2 patients had a baseline echocardiographic score of 10 and 12, respectively. Echocardiography was performed after 28 ± 14 months in 9 unselected patients with complete hemodynamic success and without restenosis at 6 months. Mitral valve area and gradient immediately after the procedure remained unchanged in the long term (1.9 ± 0.2 vs 1.8 ± 0.2 cm^2, and 4.9 ± 2.7 vs 6.1 ± 3.2 mm Hg, respectively; p = NS).

The patients aged $\geq$70 years were compared with 96 consecutive patients aged <70 years without significant aortic stenosis dilated before 1990 to analyze long-term follow-up. Baseline and post-BMC characteristics of these 96 patients were similar to those of the 156 remaining patients aged <70 years who were dilated since 1990. The overall outcome of these 96 patients included elective or urgent surgery in 7 (7%) and death in 8 (8%), including 1 perioperative (mitral valve replacement for restenosis at 2 years) and 2 noncardiac deaths; the survival rate at 3 years was 92% in these patients versus 70% in those aged $\geq$70 years ($p < 0.001$) (Figure 1).

DISCUSSION

This study shows that BMC in an older population has an increased risk of morbidity and mortality compared with in a younger one. This can be explained in part by a longer evolution of the disease, reflected by the higher incidence of atrial fibrillation and New York Heart Association class III or IV before BMC in older patients, which were reported as independent predictors of worse prognosis in previous studies.[17,18] The rate of uncompleted procedures was greater in older than in younger patients (15 vs 4%; $p < 0.05$). Technical difficulties were probably related to larger left atrial diameters and more abnormal mitral valve morphology, which impair the proper positioning of the balloon across the mitral valve. All patients aged $\geq$70 years would have needed mitral replacement, because of an important alteration of the mitral valve apparatus. On the basis of

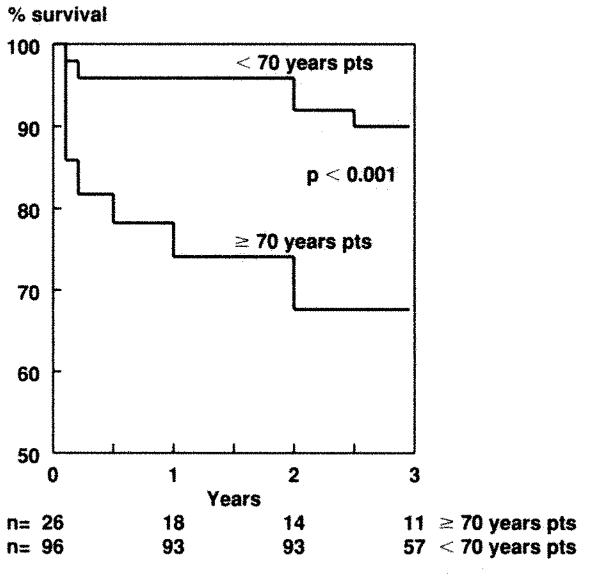

FIGURE 1. Cumulative Kaplan-Meier survival curves in 28 patients aged $\geq$70 years and 97 aged <70 years.

previous studies,[19–21] the operative mortality rate in these patients was expected to be >15% and our surgical team declined to operate on 18 of the 26 patients, because of coronary artery disease–associated valve diseases or multisystem failure. The 30-day mortality rate in this series of 26 patients undergoing BMC was 12% compared with 0.8% in patients aged <70 years.

Many previous reports[17,18,22–24] including patients with a mean age ranging from 43 to 55 years have identified echocardiographic measures of mitral valve thickening, mobility and calcification as independent predictors of acute hemodynamic results and procedural complications. In our study, explanations for the modest immediate hemodynamic results may also be related to the higher echocardiographic score in older patients, who have less pliable and more calcified valves than do younger ones. However, hemodynamic results were not correlated with the echocardiographic score, because only 3 of 26 older patients had a score <8. Predictive factors of incomplete success or hemodynamic failure in older patients were smaller mitral valve area (expressing the important alteration of the mitral valve apparatus) and greater pulmonary resistance. These predictive factors have been identified by Tuzcu et al[25] in 99 patients aged ≥65 years and by Alfonso et al[26] in 171 younger patients.

The greater cardiac mortality during the first year after BMC is in accordance with the natural history of the disease; no other therapeutic alternatives are available, and surgery is being contraindicated in most patients even before BMC. After the first year, deaths were noncardiac-related and more frequent in patients aged >70 years. In comparison, the 1-year mortality rate is 57% in patients with severe mitral stenosis with medical treatment and functional class IV (13 of 26 in our series were in class IV), and 13% for those in class II or III with atrial fibrillation.[27] At 6 months, 95% of patients aged ≥70 years had an improvement of ≥1 functional class. This improvement remained in most patients at the end of follow-up. In previous studies,[11,24,28] echocardiographic score appeared to be the most important predictive factor of restenosis and late cardiac events. In our series, restenosis was infrequent despite a high mean echocardiographic score, occurring in 2 of 16 patients (12%) with a completed successful procedure. However, baseline echocardiographic score was identified as a predictor of long-term functional improvement.

Direct comparison of BMC and surgery cannot be performed without randomized studies. Such studies appear to be impossible, because most patients aged ≥70 years had a surgical contraindication. However, BMC is an effective therapy for older patients, but has a high risk of morbidity and mortality. Furthermore, hemodynamic success and long-term cardiac survival rate are satisfactory. Therefore, BMC can be proposed as the treatment of choice in patients aged ≥70 years with symptomatic mitral stenosis and without associated significant mitral regurgitation.

REFERENCES

1. Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;87:394–402.

2. Palacios J, Block PC, Brandi S, Blanco P, Casal H, Pulido JI, Munoz S, D'Empaire G, Ortega MA, Jacobs M, Vlahakes G. Percutaneous balloon valvotomy for patients with severe mitral stenosis. *Circulation* 1987;75:778–784.

3. McKay RG, Lock JE, Safian RD, Come PC, Diver DJ, Baim DS, Berman AD, Warren SE, Mandell VE, Royal HD, Grossman W. Balloon dilation of mitral stenosis in adult patients: postmortem and percutaneous mitral valvuloplasty studies. *J Am Coll Cardiol* 1987;9:723–731.

4. Al Zaibag M, Al Kasak S, Ribeiro PA, Al Fagih MR. Percutaneous double- balloon mitral valvotomy for rheumatic mitral valve stenosis. *Lancet* 1986;1:757–761.

5. Block PC, Palacios JF, Jacobs ML, Fallon JT. Mechanism of percutaneous mitral valvotomy. *Am J Cardiol* 1987;59:178–179.

6. Reid CL, McKay CR, Chandraratna PAN, Kawanishi DT, Rahimtoola SH. Mechanisms of increase in mitral valve area and influence of anatomic features in double-balloon, catheter balloon valvuloplasty in adults with rheumatic mitral stenosis: a Doppler and two-dimensional echocardiographic study. *Circulation* 1987;76:628–636.

7. Feigenbaum H, Linback RE, Nasser WK. Hemodynamic studies before and after instrumental mitral commissurotomy: a reappraisal of the pathophysiology of mitral stenosis and the efficacity of mitral valvotomy. *Circulation* 1968;38:261–276.

8. Reyes VP, Rajn ARG, Turi ZG. Percutaneous balloon mitral valvuloplasty vs surgery: Results of a randomized clinical trial (abstr). *Circulation* 1988;78(suppl II):II–489.

9. McKay RG, Lock JE, Keane JF, Safian RD, Aroesty JM, Grossman W. Percutaneous mitral valvuloplasty in an adult patient with calcific rheumatic mitral stenosis. *J Am Coll Cardiol* 1986;7:1410–1415.

10. Palacios IF, Lock JE, Keane JF, Block PC. Percutaneous transvenous balloon valvotomy in a patient with severe calcific mitral stenosis. *J Am Coll Cardiol* 1986;7:1416–1419.

11. Lefèvre T, Bonan R, Serra A, Crépeau J, Dyrda I, Petitclerc R, Leclerc Y, Vanderperren O, Waters D. Percutaneous mitral valvuloplasty in surgical high risk patients. *J Am Coll Cardiol* 1991;17:348–354.

12. Shaw RRD, Mc Areavey D, Essop AR, Song CS. Balloon dilatation of the mitral valve for "inoperable" mitral stenosis (abstr). *Br Heart J* 1989;61:452.

13. Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072–1083.

14. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* 1988;60:299–308.

15. Bonan R, Serra A, Lefevre T. Follow-up studies: effect of balloon mitral valvotomy on symptoms, outcome, and hemodynamics. In: Bashore T, Davidson C, eds. Percutaneous Balloon Valvuloplasty and Related Techniques. Baltimore: Williams & Wilkins, 1991:218–234.

16. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. *Am J Cardiol* 1964;14:437–447.

17. NHLBI balloon valvuloplasty registry report on immediate and 30-day follow-up results. Multicenter experience with balloon mitral commissurotomy. *Circulation* 1992;85:448–461.

18. Herrmann HC, Wilkins GT, Abascal VM, Weyman AE, Block PC, Palacios IF. Percutaneous balloon mitral valvotomy for patients with mitral stenosis. Analysis of factors influencing early results. *J Thorac Cardiovasc Surg* 1988;96:33–38.

19. Scott WC, Miller DC, Haverich A, Mitchell RS, Oyer PE, Stinson EB, Jamieson SW, Baldwin JC, Shumway NE. Operative risk of mitral valve replacement: discriminant analysis of 1329 procedures. *Circulation* 1985;72(suppl II):II- 118–II-119.

20. Fremes SE, Goldman BS, Ivanov J, Weisel RD, David TE, Salerno T. Valvular surgery in the elderly. *Circulation* 1989;80(suppl I):I-77–I-90.

21. Christakis GT, Kormos RL, Weisel RD, Fremes SE, Tong CP, Hearst JA, Schwartz L, Mickleborough LL, Scully HE, Goldman BS. Morbidity and mortality in mitral valve surgery. *Circulation* 1985;72(suppl II):II-120–II-128.

22. Abascal VM, Wilkins GT, O'Shea JP, Choong CY, Palacios IF, Thomas JD, Rosas E, Newell JB, Block PC, Weyman AE. Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. *Circulation* 1990;82:448–456.

23. Reid CL, Chandraratna AN, Kawanishi DT, Kotlewski A, Rahimtoola SH. Influence of mitral valve morphology on double-balloon catheter balloon valvuloplasty in patients with mitral stenosis. *Circulation* 1989;80:515–524.

24. Vahanian A, Michel PL, Cormier B, Vitoux B, Michel X, Slama M, Enriquez Sarano L, Trabelsi S, Ben Ismail M, Acar J. Results of percutaneous mitral commissurotomy in 200 patients. *Am J Cardiol* 1989;63:847–852.

25. Tuzcu EM, Block PC, Griffin BP, Newell JB, Palacios IF. Immediate and long-term outcome of percutaneous mitral valvotomy in patients 65 years and older. *Circulation* 1992;85:963–971.

26. Alfonso F, Macaya C, Iniguez A, Banuelos C, Hernandez R, Goicolea J, Fernandez-Ortiz A, Zamorano J, Zarco P. Comparison of results of percutaneous mitral valvuloplasty in patients with large (>6 cm) versus those with smaller left atria. *Am J Cardiol* 1992;69:355–360.

27. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br Heart J* 1962;24:349–357.

28. Palacios I, Block PC, Wilkins GT, Weyman AE. Follow-up of patients undergoing percutaneous mitral balloon valvotomy. Analysis of factors determining restenosis. *Circulation* 1989;79:573–579.

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As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis; hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia; vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

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J1Z005R2(902)

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MISCELLANEOUS

Effects of Successful Cardiac Transplantation on Plasma Endothelin

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After cardiac transplantation, cyclosporine-treated patients exhibit a high incidence of systemic hypertension, the mechanism of which is not known. Endothelin, a potent vasoconstrictor peptide of endothelial origin, may be activated by cyclosporine-induced endothelial injury and therefore may mediate post-transplant hypertension. In the present study, we tested whether immunoreactive endothelin-1 could be detected by radioimmunoassay in the plasma of cardiac transplant recipients and if levels correlated with hemodynamic characteristics, cyclosporine level, or renal function as assessed by serum creatinine. Plasma endothelin was measured in 22 stable cyclosporine-treated patients 9 days to 3 years after successful orthotopic cardiac transplantation before routine hemodynamic assessment and surveillance endomyocardial biopsy. Fifteen patients were receiving chronic therapy for hypertension. Plasma endothelin-1 was 5.2 ± 1.8 pg/ml (range 3.1 to 10.5), which was increased compared with that in 12 normal subjects (1.9 ± 0.3 pg/ml; range 1.4 to 2.4); the difference was statistically significant ($p < 0.0001$). Repeated sampling in 8 patients at weekly intervals identified a persistent increase in endothelin with only modest variability. Endothelin-1 did not correlate with any hemodynamic variable, serum creatinine or cyclosporine level. Thus, endothelin-1 is increased after successful orthotopic cardiac transplantation. In the absence of discrete correlations with hemodynamic variables, serum creatinine or cyclosporine levels, both the characteristics and mechanisms for increased endothelin in recipients of cardiac transplants require further evaluation.

(Am J Cardiol 1993;71:237–240)

After cardiac transplantation, cyclosporine-treated patients have a high incidence of systemic hypertension.[1–6] This post-transplant hypertension is characterized by elevated systemic vascular resistance, normal cardiac output, and modest impairment of renal function.[5] Although the mechanism for hypertension in cyclosporine-treated patients is unknown, it does not appear to be secondary to activation of the renin-angiotensin system.[5,6] Cyclosporine-associated sympathetic changes, however, have been implicated.[7] A direct toxic effect of cyclosporine on the endothelium of the vasculature has been suggested and previous studies in animals have demonstrated that cyclosporine increases plasma and urinary endothelin, a potent vasoconstrictor peptide of endothelial origin.[8–11] Endothelin has been shown to mediate renal vasoconstriction and glomerular dysfunction in rats treated with cyclosporine.[11,12] The present study has 2 purposes: (1) to determine if circulating endothelin is elevated in cyclosporine-treated patients after successful cardiac transplantation compared with normal subjects, and (2) to determine if a correlation exists between endothelin and hemodynamic characteristics, serum creatinine or cyclosporine levels after successful cardiac transplantation.

METHODS

Study patients: The study consisted of 22 cyclosporine-treated patients 9 days to 3 years (mean 640 days) after successful orthotopic cardiac transplantation. In addition to cyclosporine, patients were receiving standard immunosuppressive therapy with azathioprine and prednisone. All patients were evaluated in the postabsorptive, nonsedated state and were undergoing routine hemodynamic assessment and surveillance endomyocardial biopsy at the time of the study. Patients exhibiting clinical evidence of severe allograft rejection such as new-onset exertional dyspnea, orthopnea, atrial or ventricular arrhythmias, recent fever, or other signs of post-transplant complications were excluded. Patients were also excluded if their endomyocardial biopsy histologic grade was >1A (focal mild rejection) according to the standard criteria described by Billingham et al.[13] The study group included 13 men and 9 women aged 47 ± 10 years (range 32 to 59). Fifteen patients (68%) were receiving antihypertensive therapy at the time of evaluation and all patients were considered New York Heart Association functional class I.

Hemodynamic evaluation: Hemodynamic studies were performed on the morning after an overnight fast immediately before endomyocardial biopsy. Cyclosporine had been given 12 hours before the study and all

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other medications, including antihypertensive therapy, were given on the morning of the study. Blood samples for endothelin, serum creatinine and cyclosporine levels were obtained from the right internal jugular vein at the time of right-sided cardiac catheterization. In 8 patients, 1 to 3 repeat evaluations (3 in 1 patient, 2 in 2 patients, and 1 in 5 patients) were performed at weekly intervals to assess the reproducibility of our endothelin assay. The protocol was approved by the Human Research Committee at the Ohio State University and written informed consent was obtained from each patient.

A flow-directed, triple-lumen catheter was positioned in the pulmonary artery under fluoroscopic guidance. Heart rate (beats per minute) was recorded from a precordial electrocardiographic lead. Pressures (mm Hg) included systemic blood pressure obtained with a brachial noninvasive cuff, right atrial pressure, pulmonary artery pressure as systolic, diastolic and mean, and pulmonary wedge pressure. Cardiac output was performed in triplicate by the thermodilution method and the average was expressed as cardiac index (liters/min/m^2). Systemic vascular resistance was calculated from the formula (mean arterial pressure − right atrial pressure) × 80/cardiac output. Pulmonary vascular resistance was derived from the formula (pulmonary artery pressure − pulmonary wedge pressure) × 80/cardiac output. These resistance values were expressed as dynes • s/cm^5. These data were compared with data from normal subjects (ages 19 to 52 years) studied under identical conditions, which have been previously reported.[14]

Endothelin assay: Blood samples for plasma endothelin-1 were obtained at the time of hemodynamic determination. The assay for measurement of plasma endothelin-1 has previously been described.[15] Four milliliters of venous blood was collected into chilled tubes containing 40% ethylenediamine-tetraacetic acid and 2,000 KIU aprotinin. Samples were kept on ice, centrifuged at 4°C with plasma stored at −80°C until analysis. Plasma samples were thawed at the time of analysis, immediately acidified with an equal volume of 0.1% trifluoroacetic acid and centrifuged at 2,000 g at 4°C for 15 minutes to remove proteolytic activity. The supernatant was extracted using Sep-Column C 18 cartridges (Penninsula Laboratories) that had been activated with 60% acetonitrile in 0.1% trifluoroacetic acid, followed by washing with 0.1% trifluoroacetic acid. After addition of samples to the cartridges, endothelin was eluted with 60% acetonitrile in 0.1% trifluoroacetic acid. Samples were dried overnight and stored at −80°C. Radioimmunoassay was performed on reconstituted samples by using rabbit antihuman endothelin-1 (Penninsula Laboratories). After overnight incubation at 4°C, ^{125}I-endothelin-1 was added, and incubation continued an additional 20 hours at 4°C. Immune complexes were precipitated with goat antirabbit serum, and the precipitates were counted for radioactivity. Cardiac transplant endothelin levels were compared with a control group of 12 normal subjects (mean age 35 ± 6 years [range 26 to 45]). The normal group consisted of 6 men and 6 women. In normal subjects, blood samples were drawn from a peripheral vein. All endothelin values were expressed as picograms per milliliter.

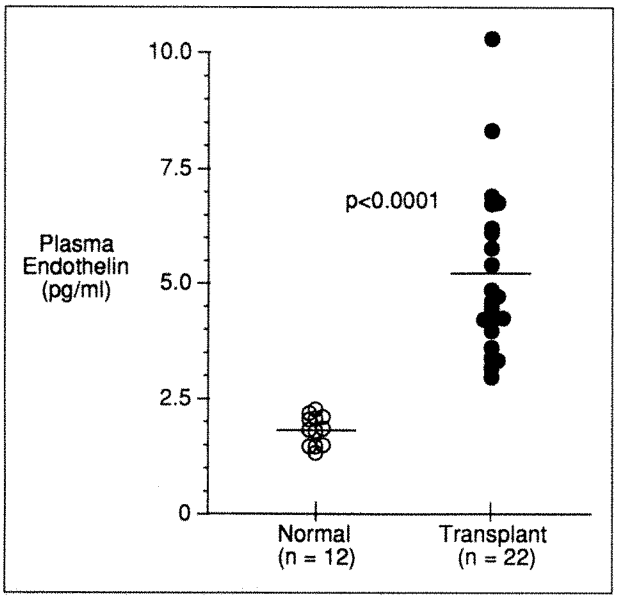

FIGURE 1. Plot shows comparison of plasma immunoreactive endothelin-1 in normal subjects and cyclosporine-treated cardiac transplant patients. There was a threefold increase of mean endothelin-1 values in transplant patients compared with normal subjects.

Statistical methods: Comparison of normal and cardiac transplant endothelin levels and hemodynamics was by 2-tailed, unpaired *t* test. To identify relevant relations, regression analysis of hemodynamic values, serum creatinine and cyclosporine levels with plasma endothelin was performed. All values are expressed as mean ± 1 SD.

RESULTS

Plasma endothelin: In normal subjects, plasma endothelin-1 was 1.9 ± 0.3 pg/ml (range 1.4 to 2.4). In cardiac transplant patients, plasma endothelin-1 was 5.2 ± 1.8 pg/ml (range 3.1 to 10.5), $p < 0.0001$ compared with normal subjects (Figure 1). Although there was a wide range of plasma endothelin in recipients of cardiac transplants, there was no overlap when compared with that in normal subjects.

Plasma endothelin: serial measurements: The plasma endothelin levels in 8 patients who had 1 to 3

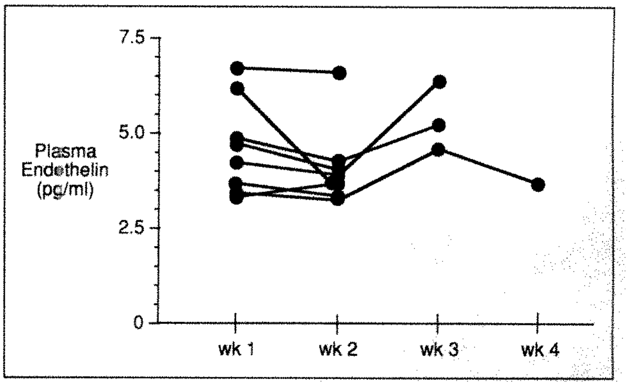

FIGURE 2. Plot shows endothelin-1 plasma levels in 8 patients who had 1 to 3 additional levels drawn at weekly intervals. At no time did levels decrease toward the normal range.

additional samples drawn at weekly intervals are shown in Figure 2. In 3 patients, there was modest variability in plasma endothelin; however, at no time did values decrease toward the normal range.

Hemodynamic and renal characteristics of cardiac transplant patients: Hemodynamic and renal characteristics of the transplant patients, compared with normal subjects, are listed in Table I. Statistically significant differences in heart rate, systemic and pulmonary pressures and resistances and serum creatinine are consistent with changes that are typical of cyclosporine-treated cardiac transplant patients.[16] Even though mean systemic arterial pressure was mildly elevated in the study group and exhibited a wide range (88 to 132 mm Hg), there was no correlation of plasma endothelin with blood pressure. Similarly, we found no significant correlation of plasma endothelin with other hemodynamic parameters including systemic and pulmonary vascular resistances. Also, endothelin level did not correlate with serum creatinine or cyclosporine level. In the 15 patients who were being treated with various antihypertensive drugs, plasma endothelin was 5.3 ± 1.4 pg/ml. This was not significantly different from the endothelin levels (5.0 ± 2.7 pg/ml) in 7 patients requiring no antihypertensive therapy.

TABLE I Hemodynamic and Renal Characteristics of Cardiac Transplant Patients and Normal Subjects

	Transplant (n = 22)	Normal (n = 7)	p Value
Heart rate (beats/min)	86 ± 9	59 ± 7	<0.0005
Arterial pressure (mm Hg)			
Systolic	143 ± 14	121 ± 11	<0.0005
Diastolic	94 ± 11	80 ± 11	<0.005
Mean	110 ± 10	94 ± 10	<0.0005
Pulmonary pressure (mm Hg)			
Systolic	33 ± 7	23 ± 5	<0.005
Diastolic	19 ± 5	12 ± 4	<0.005
Mean	23 ± 5	16 ± 4	<0.005
Right atrial pressure (mm Hg)	8 ± 4	4 ± 4	<0.025
Pulmonary wedge pressure (mm Hg)	14 ± 5	11 ± 3	<0.05
Cardiac index (liters/min/m^2)	2.7 ± 0.57	2.7 ± 0.36	NS
Stroke volume index (ml/beat/m^2)	32 ± 7	47 ± 9	<0.0005
Systemic vascular resistance (dynes s cm^{-5})	1696 ± 54	1302 ± 297	<0.05
Pulmonary vascular resistance (dynes s cm^{-5})	149 ± 84	79 ± 30	<0.025
Serum creatinine (mg/dl)	1.4 ± 0.5	1.0 ± 0.1	<0.025

DISCUSSION

We have demonstrated that plasma endothelin-1 is significantly elevated in cyclosporine-treated cardiac transplant patients compared with normal subjects. The absence of a correlation between endothelin level and mean arterial pressure, systemic vascular resistance, or other hemodynamic parameters contrasts with our findings in patients with congestive heart failure in whom circulating endothelin-1 was closely related to pulmonary hemodynamics.[15] However, this observation does not detract from endothelin as a possible mediator of cyclosporine-associated hypertension, since the relation between circulating endothelin and its biologic activity in specific vasoconstrictive disorders remains poorly defined. Endothelin may activate other neurohormonal vasoactive systems, thus complicating the relation between measured plasma endothelin and biologic effect. Nevertheless, it has recently been shown in an animal model that a twofold increase in endothelin plasma concentration can have significant biologic action including augmentation of renal and systemic vascular resistances.[17] Therefore, the observations from the current study are intriguing in that circulating endothelin-1 was found to be uniformly elevated in a patient population where systemic hypertension is prevalent and a frequent cause of morbidity.

A potential role for endothelin as a mediator of cyclosporine-associated hypertension and renal dysfunction has previously been suggested.[10–12] Although the mechanism governing endothelin synthesis and release from the endothelium has not been completely defined, prior studies have identified increased messenger ribonucleic acid activity for preproendothelin after endothelial damage.[18,19] It is by this mechanism that cyclosporine may augment endothelin activity. Zoja et al[8] reported that exposure of endothelial cells in vitro to different concentrations of cyclosporine results in a time- and dose-dependent cellular injury. Lau et al[9] also identified a toxic effect of cyclosporine on cultured rat microvascular endothelial cells. The administration of cyclosporine to rats has been shown to increase urinary excretion of endothelin-1 and its precursor, big-endothelin.[10] Perico et al[12] reported that endothelin mediates the renal vasoconstrictive effect of cyclosporine in rats. This effect was reversed by antiendothelin antibody. Other investigators[20] found that cyclosporine stimulates synthesis of endothelin in human endothelial cell tissue culture. Our finding that plasma endothelin-1 is significantly elevated in cyclosporine-treated cardiac transplant patients is consistent with these observations and further supports the hypothesis that the vasoconstrictive effect of cyclosporine may be in part mediated by endothelin. However, our results do not agree with those recently reported by Edwards et al.[21] These investigators compared endothelin levels in cardiac transplant patients treated with and without cyclosporine. Despite a high incidence of hypertension in the cyclosporine-treated group, plasma endothelin levels between groups were not statistically different. Ideally, post-transplant groups with and without cyclosporine should be further compared. The influence of prednisone or azathioprine, or both, on endothelin and the development of hypertension also cannot be excluded, but a role for these agents has not been suggested from published reports.[1,5] Although previous studies have shown that endothelin has a significant effect on renal hemodynamics and may mediate cyclosporine-induced glomerular dysfunction,[11,12] we were unable to identify a correlation between plasma endothelin and serum creatinine, consistent with previous publications.[22,23]

The present study does not exclude the possibility that increased plasma endothelin after cardiac transplantation is related to elevated pretransplant levels. It is clear that endothelin is significantly elevated in patients with congestive heart failure.[15,23] However it has previously been shown that other abnormal neurohormonal indexes associated with heart failure tend to decrease after cardiac transplantation.[24–26] Starling et al[26] showed that atrial natriuretic peptide levels decline significantly after reversal of heart failure by cardiac transplantation. It is probable that endothelin acts in a similar manner but serial measurements of endothelin before and early after transplant must be obtained to definitively address this issue.

The method used in this study for collection and measurement of endothelin has previously been reported by our laboratory.[15] The normal values in this study are consistent with those reported by other investigators.[18,21] The stability of endothelin levels in specific patients over a 1- to 3-week period (Figure 2) further supports the reliability of our assay. A potential limitation of our method relates to the different sites from which blood collections were drawn in the 2 study groups. A peripheral venous site was used in normal subjects, whereas central venous blood was collected in transplant patients. Clearance studies of endothelin-1 have been performed and the data indicate that pulmonary circulation accounts for most of endothelin clearance.[27] Therefore, it is unlikely that a significant difference in endothelin concentration exists between peripheral venous and internal jugular venous blood.

REFERENCES

1. Starling RC, Cody RJ. Cardiac transplant hypertension. *Am J Cardiol* 1990;65:106–111.

2. Ozdogan E, Banner N, Fitzgerald M, Musumeci F, Khaghani A, Yacoub M. Factors influencing the development of hypertension after heart transplantation. *J Heart Transplant* 1990;9:548–553.

3. Olivari MT, Antolick A, Ring WS. Arterial hypertension in heart transplant recipients treated with triple-drug immunosuppressive therapy. *J Heart Transplant* 1989;8:34–39.

4. Luke RG. Pathophysiology and treatment of post-transplant hypertension. *J Am Soc Nephrol* 1991;2:S37–S44.

5. Thompson ME, Shapiro AP, Johnsen AM, Itzkoff JM, Hardesty RL, Griffith BP, Bahnson HT, McDonald RH, Hastillo A, Hess M. The contrasting effects of cyclosporine-A and azathioprine on arterial blood pressure and renal function following cardiac transplantation. *Int J Cardiol* 1986;11:219–229.

6. Bellet M, Cabrol C, Sassano P, Léger P, Corvol P, Ménard J. Systemic hypertension after cardiac transplantation: effect of cyclosporine on the renin- angiotensin-aldosterone system. *Am J Cardiol* 1985;56:927–931.

7. Scherrer U, Vissing SF, Morgan BJ, Rollins JA, Tindall RSA, Ring S, Hanson P, Mohanty PK, Victor RG. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990;323:693–699.

8. Zoja C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G. Cyclosporine-induced endothelial cell injury. *Lab Invest* 1986;55:455–462.

9. Lau DEW, Wong KL, Hwang WS. Cyclosporine toxicity on cultured rat microvascular endothelial cells. *Kidney Int* 1989;35:604–613.

10. Benigni A, Perico N, Ladny JR, Imberti O, Bellizzi L, Remuzzi G. Increased urinary excretion of endothelin-1 and its precursor, big-endothelin-1, in rats chronically treated with cyclosporine. *Transplantation* 1991;52:175–177.

11. Kon V, Sugiura M, Inagami T, Harvie BR, Ichikawa I, Hoover RL. Role of endothelin in cyclosporine-induced glomerular dysfunction. *Kidney Int* 1990;37:1487–1491.

12. Perico N, Dadan J, Remuzzi G. Endothelin mediates the renal vasoconstriction induced by cyclosporine in the rat. *J Am Soc Nephrol* 1990;1:76–83.

13. Billingham ME, Cary NRB, Hammond ME, Kemnitz J, Marboe C, McCallister HA, Snovar DC, Winters GL, Zerbe A. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: heart rejection study group. *J Heart Transplant* 1990;9:587–593.

14. Cody RJ, Atlas SA, Laragh JH, Kubo SH, Covit AB, Ryman KS, Shaknovich A, Pondolfino K, Clark M, Camargo MJF, Scarborough RM, Lewicki JA. Atrial natriuretic factor in normal subjects and heart failure patients. Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. *J Clin Invest* 1986;78:1362–1374.

15. Cody RJ, Haas GJ, Binkley PF, Capers Q, Kelley R. Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. *Circulation* 1992;85:504–509.

16. Starling RC, O'Dorisio TM, Malarkey WB, Murray KD, Myerowitz PD, Cody RJ. Preserved atrial natriuretic peptide secretory function after cardiac transplantation. *Am J Cardiol* 1991;68:237–241.

17. Lerman A, Hildebrand FL, Aarhus LL, Burnett JC. Endothelin has biological actions at pathophysiological concentrations. *Circulation* 1991;83:1808–1814.

18. Lerman A, Hildebrand FL, Margulies KB, O'Murchu B, Perrella MA, Heublein DM, Schwab TR, Burnett JC. Endothelin: a new cardiovascular regulatory peptide. *Mayo Clin Proc* 1990;65:1441–1455.

19. Yoshizumi M, Kurihara H, Sugiyama T, Takaku F, Yanagisawa M, Masaki T, Yazaki Y. Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. *Biochem Biophys Res Commun* 1989;161:859–864.

20. Bunchman TE, Brookshire CA. Cyclosporine-induced synthesis of endothelin by cultured human endothelial cells. *J Clin Invest* 1991;88:310–314.

21. Edwards BS, Hunt SA, Fowler MB, Valantine HA, Anderson LM, Lerman A. Effect of cyclosporine on plasma endothelin levels in humans after cardiac transplantation. *Am J Cardiol* 1991;67:782–784.

22. Shichiri M, Hirata Y, Ando K, Emori T, Ohta K, Kimoto S, Ogura M, Inoue A, Marumo F. Plasma endothelin levels in hypertension and chronic renal failure. *Hypertension* 1990;15:493–496.

23. McMurray JJ, Simon GR, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. *Circulation* 1992;85:1374–1379.

24. Levine TB, Olivari MT, Cohn JN. Effects of orthotopic heart transplantation on sympathetic control mechanisms in congestive heart failure. *Am J Cardiol* 1986;58:1035–1040.

25. Olivari MT, Levine TB, Ring WS, Simon A, Cohn JN. Normalization of sympathetic nervous system function after orthotopic cardiac transplant in man. *Circulation* 1987;76:V62–V64.

26. Starling RC, O'Dorisio TM, Cody RJ. Rapid reduction but lack of normalization of atrial natriuretic peptide levels in patients with congestive heart failure after cardiac transplantation. *Am Heart J* 1991;122:258–261.

27. Sirvio ML, Metsarinne K, Saijonmaa D, Fyhrquist F. Tissue distribution and half-life of ^{125}I-endothelin in the rat: Importance of pulmonary clearance. *Biochem Biophys Res Commun* 1990;167:1191–1195.

Gender Independence of Ambulatory Electrocardiographic Monitoring in Predicting Perioperative Cardiac Risk

Lee A. Fleisher, MD, Stanley H. Rosenbaum, MD, Ann H. Nelson, RN, and Lynda E. Rosenfeld, MD

Perioperative ambulatory electrocardiographic (ECG) monitoring for myocardial ischemia has been shown to be useful in predicting postoperative morbid cardiac events, and postoperative myocardial ischemia was found to be the strongest predictor of perioperative cardiac morbidity in 454 high-risk patients undergoing noncardiac surgery.[1–3] The populations studied were either comprised largely of men, or women were not evaluated separately. Because of concern that prediction of cardiac risk in women may not be definable by studies performed in predominantly male populations, and because the sensitivity and specificity of exercise ECG changes (including ST-segment depression) for detecting coronary artery disease are lower in women than in men,[4] we examined the usefulness of preoperative silent ischemia identified by ambulatory monitoring by gender.

In all, 198 patients (91 women and 107 men) were studied, 146 of whom comprised the database of our previously reported study.[3] All patients either had documented coronary artery disease (prior myocardial infarction or angina), were undergoing arterial vascular procedures or had ≥ 2 of the following risk factors: hypertension (as determined by prior diagnosis or the use of antihypertensive medication, or both), diabetes, hypercholesterolemia (serum cholesterol >240 mg/dl), age >70 years and cigarette smoking (>15 pack-years). Informed consent was obtained, as approved by the Yale University School of Medicine Human Investigation Committee.

Study patients were monitored using a calibrated amplitude-modulated ambulatory ECG monitor (SpaceLabs model 90205, Redmond, Washington) with modified bipolar leads V_1 and V_5. Ambulatory ECG recordings obtained with lead V_5 were analyzed at the end of the monitoring period for ST-segment changes on a SpaceLabs FT2000 computerized analysis system, and 24-hour ST-segment and heart rate trends were plotted. All significant changes observed in the trend plots were printed at 25 mm/s, and ECG strips were reviewed by 2 investigators who were unaware of clinical outcome. Two patients with a normal baseline electrocardiogram who had persistent, nonspecific ST abnormalities on the ambulatory electrocardiogram were excluded because of concern that these changes may not be myocardial ischemia. An ischemic episode by ECG criteria was defined as either ≥ 1 mm horizontal or downsloping ST-segment depression or ≥ 2 mm ST-segment elevation measured at 60 ms after the J point and persisting for ≥ 1 minute. The choice of preoperative medication, intraoperative management, postoperative duration of monitoring and analgesia were at the discretion of the primary anesthesia and surgical teams. A 12-lead electrocardiogram was obtained the morning of each day of ambulatory ECG monitoring, or more frequently if clinically indicated. Laboratory values including creatinine kinase-MB levels were obtained according to the policy of the primary physicians. Interviews of the patients were conducted by a member of the research team on the first 3 days after surgery and again on the day of discharge.

A postoperative cardiac event was defined as death from a cardiac cause, myocardial infarction as defined by new Q waves on electrocardiogram, or increased total creatinine kinase and an MB isoenzyme fraction $>5\%$ associated with new ECG changes, acute ischemic pulmonary edema (as diagnosed by the acute onset of shortness of breath with chest x-ray findings consistent with congestive heart failure and new significant ST-segment changes [either ≥ 1 mm horizontal or downsloping ST-segment depression or ≥ 2 mm ST-segment elevation measured at 60 ms after the J point or T-wave inversion on 2 leads of a 12-lead electrocardiogram]), and unstable angina (defined as new, significant but transient ST-segment changes or T-wave inversion on 2 leads of a 12-lead electrocardiogram with or without pain).

The incidence of preoperative myocardial ischemia (as defined by the aforementioned ambulatory ECG criteria) was 15% (15 of 107) in men and 18% (16 of 91) in women (p = not significant [NS] by chi-square test). Only 1 patient (woman) had ST elevation; the remainder had ST-segment depression. There was no significant difference in age between men and women (men 70 ± 10 vs women 68 ± 10 years; p = NS by chi-square). The incidence of documented coronary artery disease was 48% (51 of 107) in men and 59% (54 of 91) in women (p = NS by chi-square test), and was not a significant predictor of postoperative morbid cardiac events in either men or women. Preoperative myocardial ischemia was a significant predictor of morbid cardiac events in both men and women (Table I) ($p < 0.05$ by Fisher's exact test). In patients with preoperative myocardial ischemia on ambulatory electrocardiogram,

TABLE I Predictive Value of Preoperative Silent Ischemia by Gender

Gender	No. of Pts.	Positive Predictive Value	Negative Predictive Value
Men	107	31% (5/16)	92% (84/91)
Women	91	37% (6/16)	97% (73/75)

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the increased relative risk of postoperative cardiac morbidity was 4.06 (1.47–1.2, 95% confidence intervals) in men, and 14.06 (3.1–63.4, 95% confidence intervals) in women. Given the power of this study, these relative risk ratios are not statistically different.

In contrast to the ST-segment changes during exercise stress testing, the presence of preoperative ST-segment changes during ambulatory monitoring indicative of silent ischemia has a similar predictive value for perioperative cardiac morbidity in both men and women in this high-risk group. The high negative predictive value of preoperative ambulatory monitoring, particularly in women, suggests that in this selected, high-risk population, the absence of preoperative ischemia is an excellent predictor of good outcome, and no further evaluation is necessary. Some investigators have suggested that the difference in the predictive value of ST-segment changes during exercise ECG testing between men and women may be related to a difference in prevalence of coronary disease in the 2 cohorts. However, other investigators have shown that in a population with chest pain syndromes in which the prevalence of coronary disease is high and similar in both men and women, the predictive value of a positive ECG test was still significantly lower in women than men.[5] Even in a population with typical angina, stress electrocardiography had a lower sensitivity in women than in men for detecting coronary artery disease.[6] In contrast to exercise ECG testing performed for diagnostic purposes, our data support the notion that preoperative ECG changes during ambulatory monitoring are a valid method for perioperative risk assessment in women with an increased prior probability of cardiac disease undergoing noncardiac surgery.

REFERENCES

1. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM, SPI Research Group. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *N Engl J Med* 1990;323:1781–1788.
2. Raby KE, Goldman L, Creager MA, Cook EF, Weisberg MC, Whittemore AD, Selwyn AP. Correlation between perioperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989;321:1296–1300.
3. Fleisher LA, Rosenbaum SH, Hawes AD, Barash PG. The predictive value of preoperative silent ischemia for postoperative ischemic cardiac events in vascular and nonvascular surgical patients. *Am Heart J* 1991;122:980–986.
4. Magna C, Dei Cas L, Albertini D, Baldi G, Visioli O. Different prognostic value of exercise electrocardiogram in men and women. *Cardiology* 1978;63:312–319.
5. Barolsky SM, Gilbert CA, Faruqui A, Nutter DO, Schlant RC. Differences in electrocardiographic response to exercise in women and men: a non-Bayesian factor. *Circulation* 1979;60:1021–1027.
6. Detry JMR, Kapita BN, Cosyns J, Scottiaux B, Brasseur LA, Rousseau MF. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. *Circulation* 1977;56:756–761.

Acute Pulmonary Edema After *Tityus Serrulatus* Scorpion Sting in Children

Carlos Faria Santos Amaral, MD, Nilton Alves de Rezende, MD, and Lineu Freire-Maia, MD

Acute pulmonary edema due to scorpion toxins has been attributed to acute left ventricular failure resulting from massive catecholamine release or myocardial damage induced by the venom.[1–3] It has been proposed that pulmonary edema could also result from increased pulmonary vascular permeability produced by vasoactive substances that may be released by the venom.[4] This report presents radiologic, electrocardiographic, enzymatic, echocardiographic and histopathologic evidence that support both cardiogenic and noncardiogenic factors in the pathogenesis of acute pulmonary edema after *Tityus serrulatus* scorpion sting in children.

Six Brazilian children (aged 3 to 9 years) with severe envenomation and pulmonary edema after scorpion sting were admitted to the intensive care units of the Hospital das Clínicas (patients 1 to 5) and Hospital Maternidade Santa Rita (patient 6) from May 1987 to October 1991. The scorpions were examined and identified as Tityus serrulatus. *Data from patients 1 to 3 were partially described in a previous paper.*[5] *On admission, chest x-ray and electrocardiograms were recorded and repeated when necessary. Blood samples were obtained for pH and blood gas measurements, and biochemical and hematologic examinations. M-mode, 2-dimensional and Doppler echocardiographic examinations (Siemens Sonoline CF) were performed during the patients' stay in the intensive care unit and repeated when they returned for follow-up 3 to 20 days after discharge from the hospital.*

The diagnosis of pulmonary edema was suspected when patients presented with tachypnea associated with cough, inspiratory retraction of the intercostal spaces and supraclavicular fossae, and, on auscultation, wheezes and moist or crepitant rales were heard over 1 or both lungs. The diagnosis was confirmed when arterial pH and blood gas measurements showed hypoxemia, and chest roentgenogram revealed alveolar infiltrates over one or both lungs.

Treatment of scorpion envenoming consisted of intravenous administration of 40 ml of scorpion antivenom (FUNED, Belo Horizonte, Minas Gerais, Brazil), which are sufficient to neutralize 12 mg of the venom, followed by continuous evaluation of vital functions and electrocardiographic monitoring.[6] *Pain at the site of the sting and vomiting were treated with intravenous administration of dipyrone (an aminopyrine congener; 40 to 80 mg/kg/day) and metoclopramide (0.5 to 1 mg/kg/day), respectively. Pulmonary edema was treated with oxygen and intravenous furosemide (1 mg/kg at 6-hour intervals), and in 2 of 6 cases, intravenous administration of deslanoside (loading dose 0.02 to 0.04 mg/kg; maintenance dose 0.01 to 0.02 mg/kg/day). Mechanical ventilation was begun when*

From Servico Especial de Cardiologia e Cirurgia Cardiovascular, Hospital das Clínicas da UFMG, Av. Prof. Alfredo Balena, 110, CEP 30.130 Belo Horizonte, Minas Gerais, Brazil, and Departamento de Farmacologia, Federal University of Minas Gerais, Belo Horizonte, Brazil. Manuscript received May 11, 1992; revised manuscript received and accepted July 8, 1992.

1992 Critical Care Cardiology Scholars Recognized

In keeping with its commitment to continuing education in the medical profession, Eli Lilly and Company once again sponsored the Critical Care Cardiology Symposia, as it has since 1990.

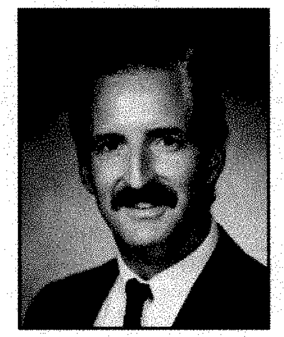
The moderator for both symposia was John M. Passmore, Jr, MD, Clinical Assistant Professor of Medicine,University of Texas Health Science Center, Houston, Texas.

Highlights of the two 1992 Symposia, held in Tampa and San Diego, were the Case Competitions, in which six Case Presentations (see below) were voted by those attended to be outstanding on the basis of their clinical interest and instructional value.

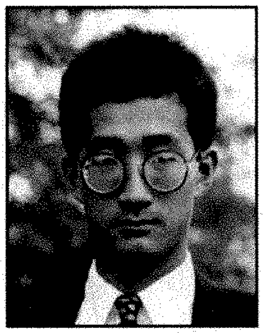
TAMPA

Orthodeoxia and Platypnea in a Young Male

Michael J. Gitter, MD
Mayo Clinic
Rochester, Minnesota



SAN DIEGO

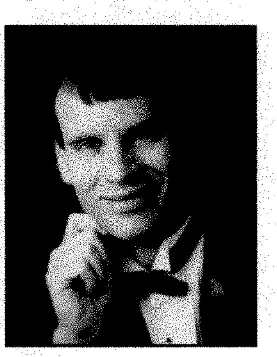


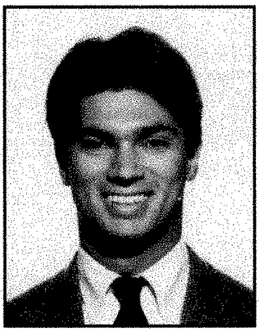
Multifactorial Shock

Jiho Han, MD
Cardiology Fellow
Medical College of Virginia
Richmond, Virginia

Acute Myocardial Infarction in a Young Female

Jonathan Safren, MD
Georgetown University Hospital
Washington, DC



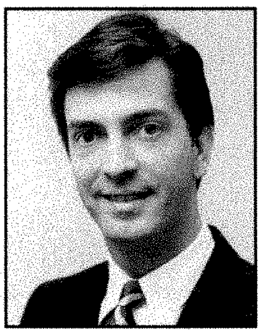


Refractory Hypoxia Complicating Acute Myocardial Infarction

Joshua M. Hare, MD
Brigham and Woman's Hospital
Boston, Massachusetts

Large Pericardial Effusion

B. Fendley Stewart, MD
University Hospital
Seattle, Washington



Peripartum Acute Myocardial Infarction in Marfan's Syndrome

John J. Santucci, MD
North Shore University Hospital
Manhassett, New York

Eli Lilly and Company wishes to thank Dr Passmore and all participants who have contributed to the success of this program

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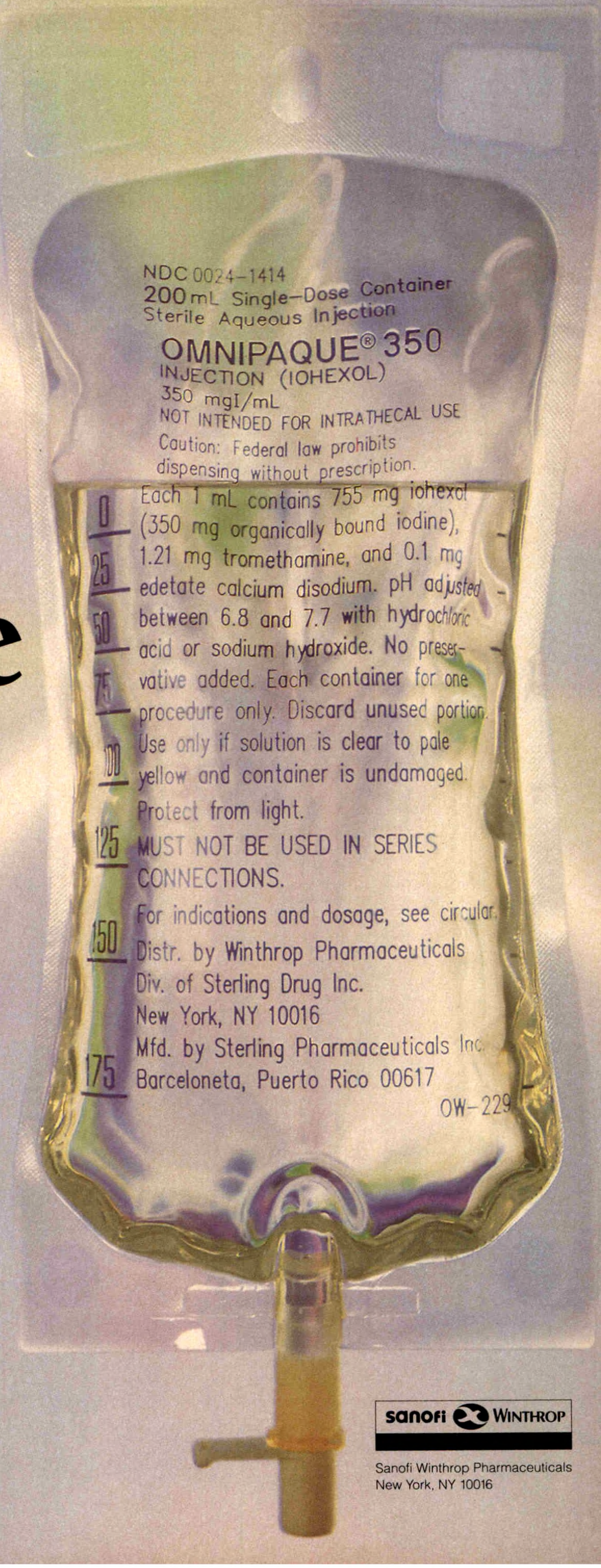

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CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General: Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease), infants, and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious, life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia, which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients: Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS—General).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including nonprescription drugs, before you are administered this drug.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine > 1.5 mg/dL, or those less than 12 months of age.

ADVERSE REACTIONS

Intravascular—General: Adverse reactions following the use of OMNIPAQUE are usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1,485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo [including dizziness and lightheadedness] (0.5%), pain (3%), vision abnormalities [including blurred vision and photomas] (2%), headache (2%), and taste perversion (1%). Others including anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication in full prescribing information.

Pediatrics: In controlled clinical trials involving 391 patients for pediatric angiocardiography, urography, and contrast-enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300 and OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).
Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).
Respiratory System: Congestion (0.3%) and apnea (0.3%).
Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).
Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media: Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above. The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria; and rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes; sneezing, and lacrimation; and rarely, anaphylactic reactions. Rare fatalities have occurred due to this or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; or *to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

CONSULT PACKAGE INSERT FOR A MORE DETAILED DISCUSSION OF ADVERSE REACTIONS FOR INTRAVASCULAR USE OF OMNIPAQUE.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION: Details are provided in the package insert.

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the aforementioned treatments did not correct hypoxemia. Positive end-expiratory pressure was initiated when an inspired oxygen concentration >60% was necessary to maintain arterial partial oxygen pressure at >50 mm Hg. Shock was treated with intravenous infusion of dobutamine or dopamine (2.5 to 20 μg/kg/min), or a combination.

The clinical, radiologic, electrocardiographic, echocardiographic and laboratory data, and the outcomes of patients are listed in Table I.

TABLE I Clinical, Radiologic, Electrocardiographic, Echocardiographic and Laboratory Data of Six Children with Pulmonary Edema After *Tityus Serrulatus* Scorpion Sting

	Patient No.					
Data	1	2	3	4	5	6
Clinical						
Age/sex	9/M	9/M	4/F	2/F	9/F	3/M
Time between sting and antivenom administration (hours)	5	13	0.5	0.5	3	0.5
Time between sting and admission to ICU (hours)	32	14	24	3	9.5	16
Arterial hypertension	0	0	0	0	0	0
Shock	0	0	0	0	+	+
Radiologic						
Cardiothoracic ratio >0.5	+	0	0	0	+	0
Distribution of lung edema						
Predominantly unilateral	0	+	+	0	+	+
Bilateral	+	0	0	+	0	0
Peripheral	+	+	+	+	+	+
Air bronchogram	0	0	+	0	+	+
Electrocardiographic						
Myocardial ischemia and injury	0	0	+	0	0	+
Sinus tachycardia (rate >130 beats/min)	+	+	+	+	+	+
Echocardiographic						
Hypokinesia of LVPW and IVS	+	+	+	0	—	+
Δd% (29–45%)	18	7	17	41	—	22
Laboratory						
CK (10–80 U/l)	120	20	64	220	—	2,830
Blood glucose (70–110 mg/dl)	175	125	82	275	161	368
Serum amylase (60–160 U/dl)	15	140	162	281	162	410
Leukocytes (5,000–10,000/mm)	25,300	20,600	12,900	28,100	39,000	26,600
Outcome	Alive	Alive	Alive	Alive	Dead	Dead*

*Necropsy was performed after death.

CK = creatine kinase enzyme; Δd% = left ventricular fractional shortening; ICU = intensive care unit; IVS = interventricular septum; LVPW = left ventricular posterior wall; + = present; 0 = absent; — = not performed.

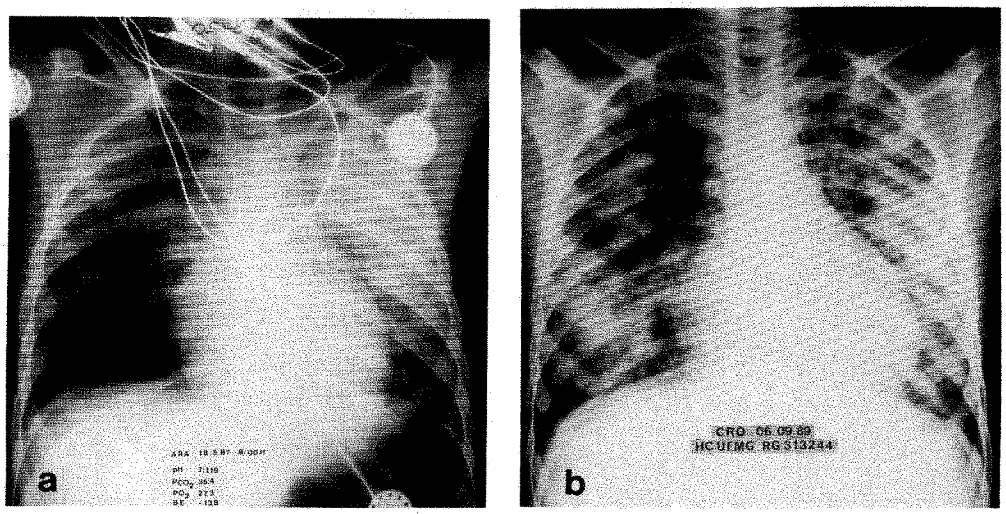

FIGURE 1. *a*, anteroposterior chest roentgenogram of patient 5 obtained 13 hours after *Tityus serrulatus* scorpion sting. Predominantly unilateral distribution of lung edema over left lung. Air bronchograms in left lung and enlargement of cardiac silhouette are present (cardiothoracic ratio >0.5). *b*, anteroposterior chest roentgenogram of patient 1 obtained 32 hours after *Tityus serrulatus* scorpion sting. Bilateral, patchy and predominantly peripheral distribution of lung edema. Cardiac silhouette is enlarged (cardiothoracic ratio >0.5).

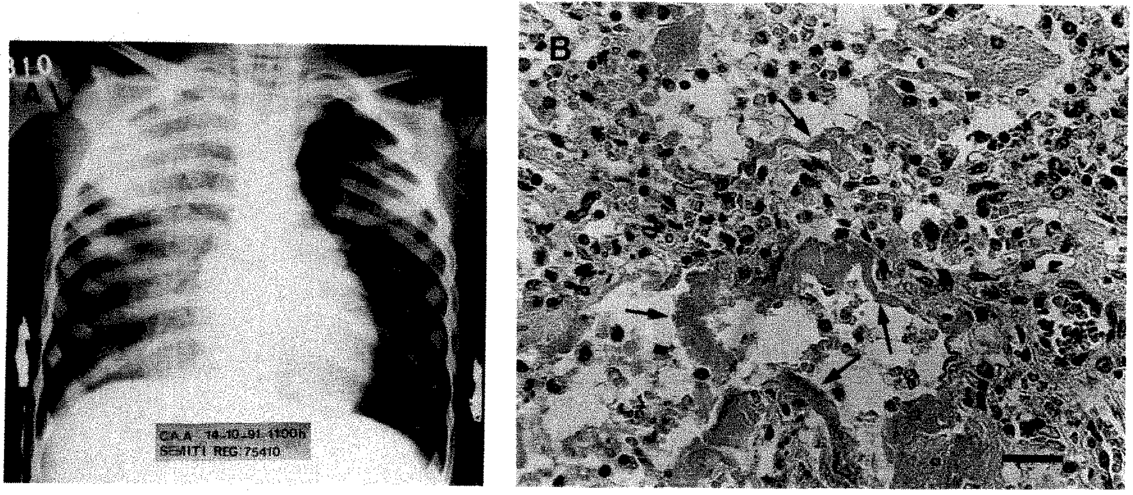

FIGURE 2. Features of lung of patient 6 who died with pulmonary edema and shock after *Tityus serrulatus* scorpion sting. *A*, anteroposterior chest roentgenogram obtained 16 hours after sting. Predominantly unilateral distribution of lung edema over right lung with air bronchograms. Mild opacification of upper left lobe with air bronchograms. Heart is not enlarged (cardiothoracic ratio <0.5). *B*, histologic picture of lung showing interstitial and intraalveolar edema, moderate mononuclear cell infiltration, fibrin exudation and hyaline membranes *(arrows)* (hematoxylin and eosin; bar = 50 μm).

Lung edema was predominantly unilateral in 4 patients and bilateral and patchy in 2 (Figure 1).

Echocardiographic examinations were performed in patients 1 to 4, and 6. All patients, except patient 4, presented with hypokinesia of the interventricular septum and left ventricular posterior wall, and decreased left ventricular fractional shortening. These changes were associated with a predominantly unilateral pulmonary edema in patients 2, 3 and 6. The echocardiographic abnormalities were no longer detected 3 to 20 days after the scorpion sting, when patients returned for follow-up.

Patients 1 to 4 survived. Patient 5 died 16 hours after the scorpion sting, and patient 6 died 57 hours after the sting; both patients needed mechanical ventilatory support with 100% oxygen and pulmonary end-expiratory pressure of 5 cm of water. Patient 6 was necropsied 10 hours after death, with family consent. Macroscopically, the right ventricle was dilated, and there was mild deviation of the interventricular septum to the left. The lungs were congested, edematous and stiffened, showing scattered areas of subpleural emphysema. Optical microscopy of the heart showed diffuse engorgement of the myocardial vessels and mild interstitial edema. Necrosis of the muscle cells was not evident. Microscopy of the lungs showed septal thickening, diffuse alveolar edema with prominent hyaline membrane, mononuclear cell infiltration and areas of alveolar collapse (Figure 2).

Previous experimental[3] and clinical[6–10] studies provided evidence that pulmonary edema due to scorpion venom is associated with left ventricular dysfunction and myocardial damage. In our series, 4 of 5 patients showed depressed left ventricular systolic function by echocardiographic examinations, 2 of 6 had cardiac enlargement on the chest x-ray, 3 of 5 had increased creatine kinase enzyme activity and 2 of 6 had electrocardiographic changes of myocardial ischemia and injury. These findings suggest that cardiac compromise may have contributed to the pathogenesis of pulmonary edema in these patients. However, patients also had radiologic, echocardiographic and histopathologic evidence that supports an increase in pulmonary vascular permeability as the pathogenetic mechanism of pulmonary edema after scorpion sting.

Patient 4 had bilateral pulmonary edema in the absence of left ventricular systolic or diastolic dysfunction assessed by means of echocardiographic-Doppler examination. Therefore, pulmonary edema in this patient may be explained by a noncardiogenic mechanism.

Radiologic data from this series showed predominantly unilateral pulmonary edema in most patients, associated with reduced left ventricular systolic function, assessed by means of echocardiographic examinations. Unilateral pulmonary edema secondary to left-sided heart failure seldom occurs in the absence of previous lung injury.[11] Therefore, the predominantly unilateral distribution of lung edema associated with left ventricular failure in these patients may be explained by a simultaneous and localized increase in pulmonary vascular permeability induced by the scorpion venom. The patchy and peripheral distribution of lung edema and the presence of air bronchograms are also radiologic features of pulmonary edema due to increased vascular permeability.[12]

Pathologic examination of the lungs of 1 patient showed macroscopic and microscopic findings compatible with a noncardiogenic acute pulmonary edema. These changes may be explained by lung damage and increased vascular permeability induced by scorpion venom.

Therefore, data from this series suggest that cardiogenic and noncardiogenic factors are involved in the pathogenesis of acute pulmonary edema after *Tityus serrulatus* scorpion sting in children. It is probable that these factors may also be important in the development of pulmonary edema due to scorpion venoms from other species.

REFERENCES

1. Freire-Maia L, Almeida HO, Cunha-Melo JR, Azevedo AD, Barroso J. Mechanism of the pulmonary edema induced by intravenous injection of scorpion toxin in the rat. *Agents Actions* 1978;8:113–118.

2. Gueron M, Yaron R. Cardiovascular manifestation of severe scorpion sting: clinicopathologic correlations. *Chest* 1970;57:156–162.

3. Gueron M, Adolph RJ, Grupp IL, Gabel M, Grupp G, Fowler NO. Hemodynamic and myocardial consequences of scorpion venom. *Am J Cardiol* 1980;45: 979–986.

4. Freire-Maia L, Campos JA. Pathophysiology and treatment of scorpion poisoning. In: Ownby CL, Odell GV, eds. Natural Toxins, Characterization, Pharmacology and Therapeutics. Oxford: Pergamon Press, 1989:130–159.

5. Amaral CFS, Lopes JA, Magalhães RA, Rezende NA. Electrocardiographic, enzymatic and echocardiographic evidence of myocardial damage after Tityus serrulatus scorpion poisoning. *Am J Cardiol* 1991;67:655–657.

6. Campos JA, Silva OA, López M, Freire-Maia L. Signs, symptoms and treatment of severe scorpion poisoning in children. In: Eaker D, Wadstron T, eds. Natural Toxins. Oxford: Pergamon Press, 1980:61–68.

7. Sofer S, Gueron M. Respiratory failure in children following envenomation by the scorpion Leiurus quinquestriatus: hemodynamic and neurological aspects. *Toxicon* 1988;26:931–939.

8. Rahav G, Weiss AT. Scorpion sting-induced pulmonary edema. *Chest* 1990; 97:1478–1480.

9. Brand A, Keren E, Reifer RM, Branski D. Myocardial damage after a scorpion sting: long-term echocardiographic follow-up. *Pediatr Cardiol* 1988;9:56–61.

10. Gueron M, Margulis G, Sofer S. Echocardiographic and radionuclide angiographic observations following scorpion envenomation by Leiurus quinquestriatus. *Toxicon* 1990;28:1005–1009.

11. Keren A, Tzivoni D, Gottlieb S, Benhorin J, Stern S. Unilateral pulmonary edema complicating acute myocardial infarction. *Am J Cardiol* 1986;57:182–183.

12. Milne ENC, Pistolesi M, Miniati M, Giuntini C. The radiologic distinction of cardiogenic and noncardiogenic edema. *Am J Roentgenol* 1985;144:879–894.

Effects of Coronary Angioplasty Using Progressive Dilation on Ostial Stenosis of the Left Anterior Descending Artery

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Percutaneous transluminal coronary dilation of left anterior descending (LAD) ostial stenoses has been considered a high-risk procedure, because of its proximity to the left main, and an increased trend toward abrupt closure.[1,2] Dilation of ostial lesions in general has not been advocated based on data[3] available on right coronary ostial stenoses, which showed an increased rate of acute complications, a low primary success rate and a relatively high restenosis rate. We retrospectively analyzed our experience in 40 consecutive patients undergoing coronary angioplasty of ostial stenosis in the LAD to test the hypothesis that progressive coronary dilation may also enable safer dilation of stenoses at the origin of the LAD (i.e., lesions in which balloon positioning causes left main occlusion).

We examined all patients from 1984 to 1991 who underwent coronary angioplasty of an ostial stenosis of the LAD and compared the results with a control group of age- and sex-matched patients undergoing coronary angioplasty of stenoses in the proximal (nonostial) or mid-LAD during the same period. For purposes of this study, ostial lesions were defined as lesions located within 0.5 cm of the orifice of the LAD, or those needing ≥1 half of the balloon being inflated within the left main coronary artery for dilation. Patients who had cardiogenic shock at the time of angioplasty, or those unsuitable for coronary bypass surgery were excluded from the study. The final study group comprised 40 patients undergoing coronary angioplasty of a native ostial LAD stenosis.

Primary angioplasty success was defined as a residual luminal diameter stenosis of ≤40% using quantitative videodensitometry. Dissection was defined according to the guidelines published by the National Heart, Lung, and Blood Institute coronary angioplasty registry.[4] A dissection was considered to be minor when it caused <50% luminal obstruction and to be major if it caused >50% obstruction. Restenosis was considered present if the luminal diameter was obstructed by >50% at follow-up angiography.[5] All stenoses were characterized according to lesion-type guidelines published by the American Heart Association/American College of Cardiology Task Force for coronary angioplasty.[6]

All patients had coronary angioplasty performed by the femoral approach using the standard over-the-wire technique. Each lesion was dilated using the progressive coronary dilation technique. This technique comprises predilating the stenosis with an undersized balloon (2.0 or 2.5 mm), followed by maximal dilation with an optimally sized balloon (3.0, 3.25, 3.5, 3.75 or 4.0 mm). The balloon catheters were exchanged over an extended wire. The wire was not withdrawn before optimal dilation in any case. For LAD ostial stenoses, the undersized balloon was inflated using 7- to 9-bar (average 8) pressure for 45 to 90 seconds, depending on the hemodynamic response to left main occlusion. Two inflations were made with the undersized balloon. The optimally sized larger balloon was inflated using 6- to 8-bar (average 7) pressure for 45 to 90 seconds depending on the hemodynamic response. Two inflations were made with the optimally sized balloon. A similar protocol was used for the control group (proximal or mid-LAD location), except that the inflation time for each balloon varied between 60 and 90 seconds.

Repeat angiography was performed in 24 of 40 patients (60%) with ostial stenosis and in 21 of 40 control patients (52%). Repeat angiography was performed at 1 to 14 months (mean 7) in the ostial stenosis study group and at 2 to 15 months (mean 6) in the control group.

The baseline clinical characteristics and angioplasty results of both groups are listed in Table I. There was no significant difference between study and control patients regarding age, degree of left ventricular dysfunction, unstable angina or recent thrombolytic therapy. Although the control group had a greater percentage of patients with hypertension, diabetes mellitus, tobacco use and multivessel disease, this did not reach statistical significance. Patients with ostial stenosis had a greater frequency of recent myocardial infarction and hypercholesterolemia; however, this did not reach statistical significance.

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TABLE I Baseline Patient Characteristics and Percutaneous Transluminal Coronary Angioplasty Results

	Ostial (n = 40)	Nonostial (n = 40)
Mean age (year)	58 ± 12	58 ± 12
Men/women	26/16	26/16
Ejection fraction (%)	43 ± 10	42 ± 8
Thrombolysis (recent)	7	8
Systemic hypertension	20	27
Diabetes mellitus	8	12
Hypercholesterolemia >240 mg/dl	15	9
Unstable angina	8	6
Cigarette smoker	16	24
Numbers of coronary arteries dilated >50% diameter stenosis		
1 vessel	19	6
>1 vessel	23	27
Myocardial infarction <4 weeks	17	12
Mean no. of stenoses dilated	2 ± 1	2 ± 1
Type A	0	17
Type B	39	23
Type C	3	2
Primary success rate	40 (100%)	39 (97.5%)
Before angioplasty stenosis (%)	86 ± 9	88 ± 8
After angioplasty stenosis (%)	11 ± 10	17 ± 10

All values not significant at $p \leq 0.05$.

The lesion characteristics and mean number of stenoses dilated during the procedure are listed in Table I. Although most patients underwent multilesion or multivessel angioplasty, the mean number of stenoses dilated was similar in both groups. Because the American Heart Association/American College of Cardiology Task Force for coronary angioplasty classification system classes all ostial stenoses as type B, this mandated a statistically lower number of type A lesions and a statistically greater proportion of type B lesions in the study group than in the control group. There was no statistically significant difference between type C lesions dilated in the 2 groups. The mean numbers of stenoses before and after coronary angioplasty, as well as the primary success rates of both groups, are listed in Table I. The primary success rate was 100% in patients with ostial stenoses versus 97.5% in the control group. Figure 1 shows the angiograms of a dilation of an LAD ostial stenosis before and after coronary angioplasty. Figure 2 demonstrates the results of a dilation of a LAD stenosis before and after angioplasty, showing total occlusion of the LAD at its origin. Although the mean stenosis rate before angioplasty was similar in both groups (86% in ostial vs 88% in control patients), that after angioplasty was greater in the control group (17 vs 1%; p = not significant) (Table I).

There was a slightly greater incidence of minor dissections in the control group (20 vs 7%; p = not significant). There was no difference in the incidence of myocardial infarction, major dissection, death, abrupt closure, and necessity of coronary artery bypass surgery between the 2 groups.

Follow-up coronary angiography was performed in 24 of 40 patients (60%) with ostial stenosis and in 21 of 40 control patients (52%). Although the mean interval before repeat angiography was slightly longer in the study group than in the control group, this did not reach

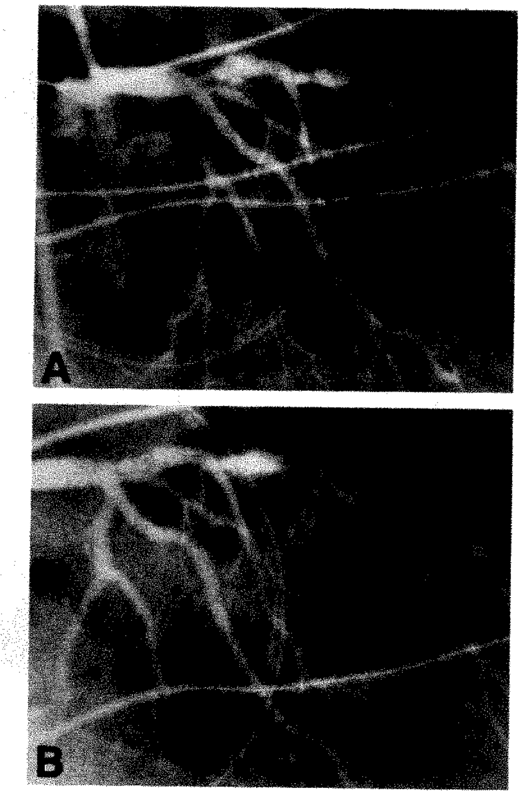

FIGURE 1. Typical example of results of angioplasty using progressive coronary dilation of ostial left anterior descending stenosis. *A*, before angioplasty. *B*, after angioplasty.

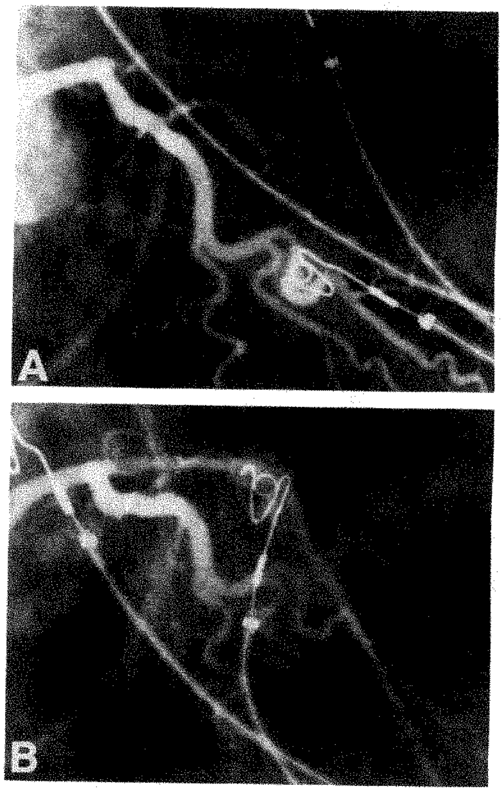

FIGURE 2. Progressive coronary angioplasty of total occlusion of left anterior descending stenosis. *A*, before angioplasty. *B*, after angioplasty.

statistical significance. The restenosis rate was 38% in both groups.

This study shows that coronary angioplasty of a native ostial LAD can be safely performed with a primary success rate virtually the same as that of a proximal or mid-native LAD. Previous studies also suggested similar results. Whereas the results of Nakhjavan et al[7] were hindered by a small sample size, our results are comparable to the preliminary observations of Simon et al[8] who reported that dilation of the origin of the LAD can be safely performed. Our primary success rate was higher than that of either study, which may either relate to evolving experience and technology or be the result of the progressive coronary dilation technique.

The acute complication rate, including incidence of dissection, abrupt closure, necessity of emergency coronary artery bypass surgery, incidence of myocardial infarction and death, was not statistically different between the 2 groups. The incidence of dissection closely paralleled that found by Simon et al.[8] In most cases in both this study and that of Simon, dissection in the area of the left main coronary artery was relatively well-tolerated without hemodynamic compromise. The incidence of emergency coronary artery bypass surgery as reported by Simon in patients undergoing coronary angioplasty of ostial stenosis was approximately 5.3%, substantially greater than that found in this study, with no patient needing coronary artery bypass surgery in either group. The incidence of coronary artery bypass surgery in this study was also less than that found by Bredlau et al[9] for all patients undergoing elective coronary angioplasty. This finding may have been influenced by the small sample size of our study. Furthermore, the incidence of myocardial infarction in this study was lower than that found by Simon. However, the overall mortality rate in patients with ostial stenosis was similar to that found by both Simon and Nakhjavan et al.[7]

Restenosis remains a limitation to the long-term benefits of coronary angioplasty. Previous studies found lesions in the LAD to have the greatest propensity for restenosis,[10,11] especially proximal versus mid- or distal LAD arteries.[8] We were unable to calculate exact restenosis rates because only 60% of study patients compared with 52% of control patients had repeat angiography. The inability to restudy all patients usually creates bias toward the restudy of sicker patients, and overestimation of restenosis rates.[12] However, regardless of this limitation, we found an identical rate of restenosis in both groups.

This study indicates that the success and complication rates for coronary angioplasty of ostial native LAD using the progressive coronary dilation technique are similar to those for the proximal or mid-native LAD. There was no incidence of major dissection, abrupt occlusion, emergency coronary artery bypass surgery or death in this series. Thus, progressive coronary dilation appears to be a safe approach for dilation of lesions in such locations. Although atherectomy and excimer laser coronary angioplasty are currently considered to be favorable alternatives for ostial lesions, no studies comparing acute success and complication rates using these techniques are available.[13] Further evaluation of the progressive coronary dilation technique for ostial lesions of the LAD is needed in larger groups of patients.

Whether the high procedural success rate and lower acute complication rate using this technique in the LAD artery extend to the ostial right coronary artery or ostial graft lesions needs to be evaluated.

REFERENCES

1. Haraphongse M, Rossall RE. Subacute left main coronary stenosis following percutaneous transluminal coronary angioplasty. *Cathet Cardiovasc Diagn* 1987;13:401–404.

2. Ellis SG, Roubin GS, King SB, Douglas JS, Weintraub WS, Thomas RG. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 1988;77:373–379.

3. Topol EJ, Ellis SG, Fishman J, Leimgruber P, Myler RK, Stertzer SH, O'Neill WW, Douglas JS, Roubin GS, King SB 3d. Multicenter study of percutaneous transluminal angioplasty for right coronary artery ostial stenosis. *J Am Coll Cardiol* 1987;9:1214–1218.

4. Dorros G, Cowley MJ, Simpson J, Bentivoglio LG, Block PC, Bourassa M, Detre K, Gosselin AJ, Gruntzig AR, Kelsey SF, Kent KM, Mock MB, Mullin SM, Myler RK, Passamani ER, Stertzer SH, Williams DO. Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung, and Blood Institute PTCA Registry. *Circulation* 1983;67:723–730.

5. Sahni R, Maniet AR, Voci G, Banka VS. Prevention of restenosis by lovastatin after successful coronary angioplasty. *Am Heart J* 1991;121:1600–1608.

6. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB 3d, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winter WL Jr. Guidelines for percutaneous transluminal coronary angioplasty: a report of the ACC/AHA Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. *J Am Coll Cardiol* 1988;12:529–545.

7. Nakhjavan FK, Goldman AP, Hutt GH, Wertheimer JH, Yazdanfar S, Maranhao V, Weiner R. Percutaneous transluminal coronary angioplasty of the "very proximal" coronary artery stenosis. *Cathet Cardiovasc Diagn* 1987;13:87–92.

8. Simon R, Amende I, Herrmann G, Reil G. Coronary angioplasty of lesion adjacent to the left main stem: results and risks (abstr). *Circulation* 1986;74(suppl II):II-193.

9. Bredlau CE, Roubin GS, Leimgruber PP, Douglas JS, King SB, Gruentzig AR. In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty. *Circulation* 1985;72:1044–1052.

10. Leimgruber PP, Roubin MB, Hollman J, Cotsonis GA, Meier B, Douglas JS, King SB Jr, Gruentzig AR. Restenosis after successful coronary angioplasty in patients with single vessel disease. *Circulation* 1986;73:710–717.

11. Roubin GS, King SB, Douglas JS. Restenosis after percutaneous transluminal coronary angioplasty: the Emory University Hospital experience. *Am J Cardiol* 1987;60:39B–43B.

12. Weintraub WS. Design considerations in the study of restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1987;60:3B–4B.

13. Robertson GC, Hinohara T, Selmon MR, Johnson DE, Simpson JB. Directional coronary atherectomy. In: Topol EJ, ed. Textbook of Interventional Cardiology. Philadelphia: W.B. Saunders, 1990:571.

Effects of Adenosine on Atrial Repolarization in the Transplanted Human Heart

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Adenosine is a naturally occurring purine metabolite that is widely used for the termination of junctional arrhythmias. Its cardiac actions are mediated by both a direct effect and a complex interaction with the autonomic nervous system. To assess the relative importance of these 2 actions in vivo, the effects of adenosine on atrial repolarization and atrioventricular (AV) conduction in the transplanted human heart were compared with those in normally innervated control subjects.

The study cohort comprised 26 patients; 12 had undergone orthotopic cardiac transplantation within the preceding 3 to 16 months (Table I). Three patients had previously documented episodes of spontaneous atrial flutter, with 1 needing cardioversion. The arrhythmia occurred in 1 patient in the early postoperative phase, whereas 2 developed symptoms late after transplantation. In 1 patient, the arrhythmia was associated with an episode of severe cardiac rejection. The electrophysiologic study was performed at the time of routine endomyocardial biopsy in this group. All patients were hemodynamically stable, with only 1 having mild cardiac rejection (Billingham classification) on right ventricular biopsy. Fourteen subjects undergoing routine diagnostic electrophysiologic study constituted the control group (Table II). Patients were studied in the postabsorptive, nonsedated state after withdrawal of all antiarrhythmic drugs for ≥5 half lives (3 months in the case of amiodarone). Written, informed consent was obtained in all cases, and the study protocol was approved by the district medical ethics committee.

A 6Fr catheter with silver-silver chloride electrodes for monophasic action potential (MAP) recording was introduced through the femoral or internal jugular vein and positioned under fluoroscopic guidance in firm ap-

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TABLE I Effects of Adenosine on Atrial Repolarization and Atrioventricular Conduction on Transplant Group

				MAP Shortening					AV Block	
Pt.	Age (yr) & Sex	TFT (mos)	Imm.	Before	After	% Change	Onset	Duration	Onset	Duration
1	60M	16	Aza., CyA, P	225	132.5	41	20	30	15.5	6
2	38M	9	Aza., CyA, P	200	155	22.5	10.5	15	15	10.5
3	53M	6	Aza., CyA	275	265	3.6	13.5	3	No AV block	
4	56M	11	Aza., CyA	225	135	40	10.5	15	13.5	10.5
5	51M	7	Aza., CyA	230	125	45.6	9	25.5	12	12
6	56M	7	Aza., CyA, P	240	150	37.5	16.5	16.5	19.5	7
7	62M	11	Aza., CyA	200	155	22.5	9	25	19.5	10.5
8	53M	6	Aza., CyA	235	170	27.6	9	25.5	10.5	15
9	54M	11	Aza., CyA	267.5	180	32	13.5	22.5	22.5	10.5
10	50M	3	Aza., CyA, P	285	230	17.5	24	12	No AV block	

AV = atrioventricular; Aza. = azathioprine; CyA = cyclosporin; Imm. = immunosuppressive drug regimen; MAP = monophasic action potential; P = prednisolone; TFT = time from transplantation.

TABLE II Effects of Adenosine on Atrial Repolarization and Conduction in Control Subjects

			MAP Shortening					AV Block	
Pt.	Age (yr) & Sex	Diagnosis	Baseline	After	% Change	Onset	Duration	Onset	Duration
1	60F	AVNRT	215	180	16.2	10.8	12	14.4	8.4
2	20M	Postop.	260	220	15.3	10.8	12	19.2	3
3	46M	Postop.	215	215	0	0	0	No AV block	0
4	22M	WPW	184	180	2.2	16	3	Preexcited	—
5	33M	WPW	215	197.5	8.1	20.4	8.4	Preexcited	—
6	55F	AVNRT	235	215	8.5	16.8	9.6	No AV block	0
7	61M	VT	280	205	26.7	7.5	22.5	16.5	2
8	18M	WPW	190	175	7.9	12	9	Preexcited	—
9	60M	WPW	220	147.5	32.9	21.6	13.2	21.6	7.2
10	29M	Syncope	220	135	38.6	12	9	No AV block	0
11	24M	WPW	220	167.5	23.8	?	7.5	Preexcited	—
12	28F	Concealed WPW	285	195	31.5	9	3	10	3
13	64M	WPW	217.5	200	8.0	9	20	15.5 (block in AV node and pathway)	7.5
14	38M	WPW	217.5	200	8.0	18	12	Preexcited	—

AVNRT = atrioventricular nodal reentrant tachycardia; Postop. = postoperative division of accessory pathway; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome; other abbreviations as in Table I.

position to the lateral wall of the right atrium until a satisfactory MAP recording was obtained. Recording of the MAP using this contact catheter technique has been shown to accurately indicate the onset, duration, configuration and relative changes in amplitude of the transmembrane action potentials. The signals were amplified using a commercially available differential, direct-current–coupled pre-amplifier with a frequency response of 0 to 5,000 Hz (EP Technologies Inc.). The signal was displayed on a Siemens-Elema Mingograf chart recorder at a paper speed of 200 mm/s. Signals with a stable baseline of >4 mV amplitude and sharp upstroke were considered satisfactory.

After 3 minutes of constant rate atrial pacing at a cycle length of 500 ms to enable stabilization of the MAP, 6 mg of adenosine were administered by rapid intravenous bolus through a forearm vein, followed by a 5 ml bolus of physiologic saline solution. MAP dura-

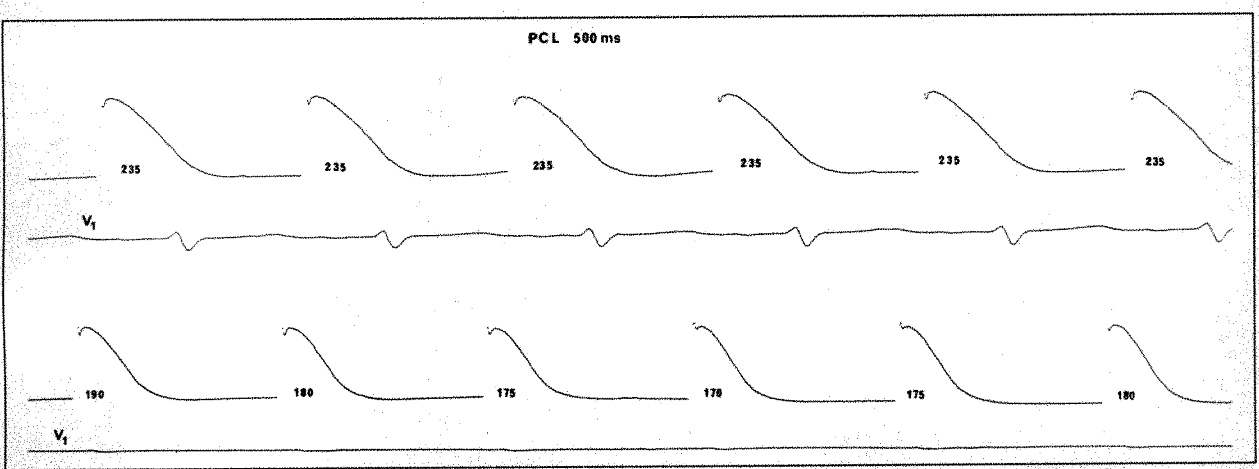

FIGURE 1. Right atrial monophasic action potential and surface lead V_1 *(top)* at baseline and *(bottom)* after 6 mg of adenosine (note complete atrioventricular block with ventricular standstill). *Inset numbers* represent 90% repolarization time for each monophasic action potential. PCL = paced cycle length.

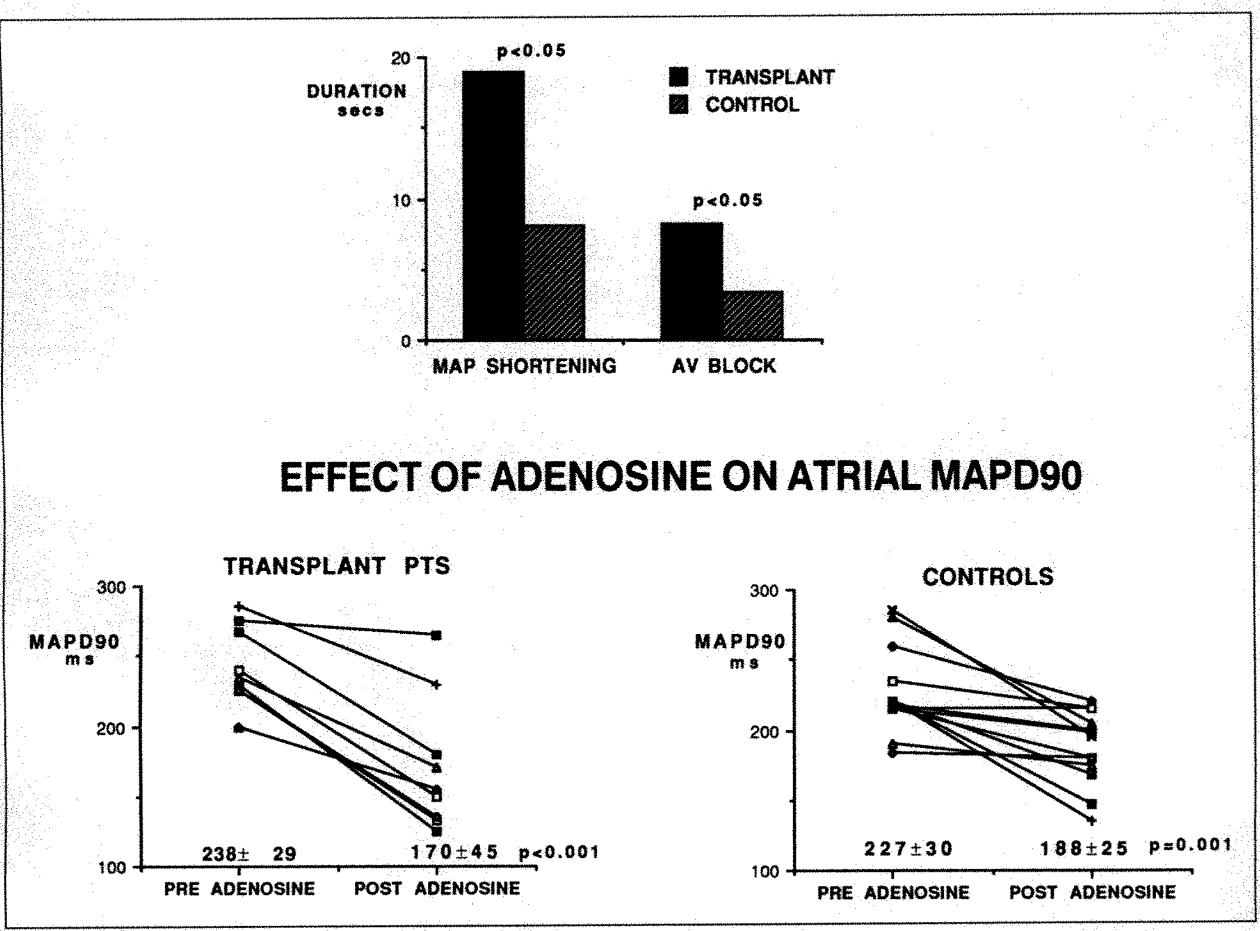

FIGURE 2. The effect of adenosine on atrial monophasic action potential (MAP) duration and atrioventricular (AV) block in transplant patients and control subjects. MAPD90 = MAP duration at 90% repolarization.

tion at 90% repolarization ($MAPD_{90}$) was measured in all cases. The baseline $MAPD_{90}$ was averaged over 10 beats before the administration of adenosine and was then measured every 1.5 seconds for 1 minute or until the loss of constant atrial capture due to either spontaneous atrial ectopics or an accelerating sinus rate. The onset of shortening of the MAP was considered the point at which $MAPD_{90}$ shortened by >5 ms from the minimum baseline value, and the offset was similarly defined.

The effect of adenosine was compared in the same patient before and after adenosine using paired t *tests. For comparisons between the transplant and control groups, the data were normalized and then compared using unpaired* t *tests. A p value <0.05 was considered statistically significant.*

Satisfactory MAP recordings were obtained in 10 of 12 transplant patients. In 1 patient, satisfactory recordings could be obtained from the recipient atrium only. In 1 patient, no satisfactory recording could be obtained from either the donor or recipient atrium. Satisfactory MAP recordings were obtained in all 14 patients in the control group.

Adenosine markedly shortened the atrial MAP in both groups (transplant 238 ± 29 to 170 ± 45 ms [p <0.001], and control 227 ± 29 to 188 ± 25 ms [p = 0.001]) (Figures 1 and 2). The percent shortening of $MAPD_{90}$ in the transplant group was significantly greater than in the control group (28.9 ± 12.8% vs 16.2 ± 12.3%; p <0.05). There was no difference between the 2 groups in the time of onset of MAP shortening (13.5 ± 5.1 vs 12.7 ± 5.8 seconds). However, the duration of MAP shortening was significantly greater in the transplant than control group (19 ± 8.1 vs 1.1 ± 7.5 seconds; p <0.05). AV block occurred in 8 of 10 patients in the transplant group and in 6 of 9 in the control group who did not have evidence of ventricular preexcitation (Figure 2). The time to onset of AV block was similar in the 2 groups (16.0 ± 4.1 vs 16.2 ± 4.0 seconds). The duration of AV block was significantly greater in transplant patients (8.2 ± 4.9 vs 3.4 ± 3.4 seconds; p <0.05). In the transplant group, 6 of the 8 patients had AV block for >10 seconds, whereas the longest period of AV block in the control group was 8 seconds. We originally intended to study 2 doses of adenosine—6 and 12 mg—these being the recommended doses in the nontransplant population. However, because of the profound effects of 6 mg of adenosine on AV conduction, it was not considered safe to administer the 12 mg dose in the absence of backup ventricular pacing.

The results show that in the transplanted human heart, the donor atrium has increased sensitivity to exogenous adenosine, which is manifest as a greater and more prolonged shortening of the atrial MAP. Furthermore, we confirmed the previously reported supersensitivity of AV nodal tissue to adenosine.[1] Denervation supersensitivity to adrenergic and cholinergic neurotransmitters is thought to be due to either an increase in surface receptor density or upregulation of postreceptor secondary messengers.[2,3] Although adenosine is not regarded as a classical neurotransmitter, its electrophysiologic properties in supraventricular tissues are mediated by the same receptor-linked G proteins as is acetylcholine.[4] These G proteins activate a specific outward potassium current and exert a moderate inhibitory effect on the catecholamine-stimulated inward calcium current. This results in marked shortening of action potential duration, hyperpolarization of the cell membrane, inhibition of automaticity, and a decrease in contractility. Upregulation of these shared G proteins is perhaps the most likely explanation for the adenosine supersensitivity demonstrated in this study.

The results of this study have several physiologic and possible clinical implications. First, when adenosine is administered by intravenous bolus, the initial direct effects on the heart are followed by a phase of reflex sympathetic activation. This study demonstrates that the shortening of the MAP observed in the nondenervated heart is a direct myocardial effect and is not dependent on reflex sympathetic activation. Second, it has been suggested that in the transplanted heart, the exaggerated bradycardic response of the sinus node and dromotropic response of the AV node to adenosine are not due to increased myocardial sensitivity, but simply reflect an absence of adenosine-induced sympathetic activation. This is a valid argument for the effects on the sinus and AV nodes, where adenosine and adrenergic stimulation exert opposing effects. However, the effects of the 2 stimuli on atrial repolarization are concordant (i.e., they both shorten the atrial MAP). Therefore, the absence of reflex stimulation would tend to minimize rather than maximize the effect of adenosine on the donor atrium. The exaggerated shortening of the MAP in the donor atrium demonstrates that the supersensitivity of the transplanted heart to adenosine is due to a direct increase in myocardial sensitivity.

Recent observations in the innervated heart suggest that endogenously released adenosine may exert measurable cardiac electrophysiologic effects, even in nonhypoxic conditions.[5] In the transplanted heart, the exaggerated response to endogenous adenosine may have a role in the development of arrhythmias, particularly in cases associated with increased adenosine release such as hypoxia and possibly rejection. Thus, the sinus bradycardia associated with acute cardiac rejection has been successfully treated with the purine antagonist theophylline.[6] Similarly, the profound effects of adenosine on atrial repolarization could have a contributory role in the reentrant atrial arrhythmias that continue to represent a clinical problem even in patients treated with cyclosporine. This suggests the possibility that theophylline or other, more specific, purinergic antagonists could be used to treat recurrent atrial flutter in this patient group. Finally, we agree with the recent recommendation that a lower initial dose of intravenous adenosine should be used in transplant recipients; we would suggest 25 to 50% of the standard dose recommended for nontransplant patients.

REFERENCES

1. Ellenbogen KA, Thames MD, DiMarco JP, Sheehan H, Lerman BB. Electrophysiologic effects of adenosine in the transplanted human heart. Evidence of super-

sensitivity. *Circulation* 1990;81:821–828.
2. Yusuf S, Theodoropoulus S, Mathias CJ, Dhalla N, Wittes J, Mitchell A, Yacoub M. Increased sensitivity of the denervated transplanted human heart to isoprenaline both before and after B blockade. *Circulation* 1987;75:696–704.
3. Kaseda S, Zipes D. Supersensitivity to acetylcholine of canine sinus and AV nodes after parasympathetic denervation. *Am J Physiol* 1988;255:H534–H539.
4. Belardinelli L, Isenberg G. Isolated atrial myocytes: adenosine and acetylcholine increase potassium conductance. *Am J Physiol* 1983;244:H734–H737.
5. Lerman BB, Wesley RC, Belardinelli L. Electrophysiologic effects of dipyridamole on atrioventricular nodal conduction and supraventricular tachycardia. *Circulation* 1989;80:1536–1543.
6. Ellenbogen KA, Szentpetery S, Katz MR. Reversibility of prolonged chronotropic dysfunction with theophylline following orthotopic cardiac transplantation. *Am Heart J* 1988;116:202–206.

Atrial Flutter Causes Pseudo Late Potentials on Signal-Averaged Electrocardiogram

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Signal-averaged electrocardiography (SAECG) is a useful tool for determining which patients are at risk for sustained ventricular tachycardia.[1–3] In patients at risk for sustained ventricular tachycardia, SAECG often shows high-frequency and low-amplitude electrical activity at the terminal portion of the QRS complex.[4–6] This electrical activity is thought to be due to slow conduction in scarred or abnormal ventricular myocardial tissue and is usually not apparent on the standard 12-lead surface electrocardiogram.[7–10] During atrial flutter, flutter waves may occur before, during or after ventricular systole. Atrial flutter waves that occur during ventricular diastole frequently appear as "sawtooth" waves on the standard 12-lead electrocardiogram, particularly in the inferior limb or anterior chest leads. However, atrial flutter waves that occur during ventricular systole may be obscured by the QRS complex. To test the hypothesis that atrial flutter waves that coincide with the terminal portion of the QRS complex cause low-amplitude electrical activity and thus result in a pseudo late potential on the electrocardiogram, we performed SAECG in 9 patients during atrial flutter and normal sinus rhythm.

All SAECGs were performed by the same technician. The mean interval between SAECG performed during atrial flutter and after conversion to sinus rhythm was 2.7 ± 1 days (range 4 hours to 22 days). SAECG was performed with the Arrhythmia Research Technology (ART-EPX 1200) system. Three orthogonal leads (x, y and z) were used. At least 200 beats were recorded and averaged on each occasion. A template recognition created by the first 8 beats was used to reject noise and ectopic beats. All signals were digitized and amplified before being filtered with a bidirectional Butterworth filter at a band-pass of 40 to 250 Hz. All recordings were obtained at a noise level <0.5 μV. A computer algorithm identified the onset and offset of the initial and terminal portions of both the filtered and unfiltered QRS complex. This was verified by 2 blinded investigators. The duration of the filtered QRS complex, of low-amplitude signal (<40 μV) at the terminal portion of the QRS complex, and the root-mean-square of the last 40 ms of the filtered QRS complex were also determined. Late potentials were considered present if any 2 of the following 3 criteria were satisfied: (1) filtered QRS complex duration >120 ms, (2) low-amplitude signal duration >40 ms, and (3) root-mean-square of the terminal 40 ms of the QRS complex <25 μV.

The onset and offset of the filtered atrial flutter and P waves in each orthogonal lead were identified by 2 observers, and the flutter wave duration was calculated. The time of the flutter waves relative to the filtered QRS complex was also analyzed, and flutter waves were classified as occurring at the onset, during or at the terminal portion of the QRS complex. A flutter wave was classified as occurring during the QRS complex only if both the onset and offset of the flutter wave were within the filtered QRS complex. Student's paired t *test was used to detect any differences before and after conversion to sinus rhythm. Differences with p values <0.05 were considered significant.*

The mean age of the patients was 60 ± 15 years (range 39 to 69). No patient had a history of sustained ventricular tachycardia. Four patients had left ventricular hypertrophy due to hypertension, 2 had dilated cardiomyopathy, 1 had a prosthetic mitral valve replacement, 1 had recurrent syncope, but no inducible ventricular tachyarrhythmias at electrophysiologic study, and 1 had a history of aborted sudden cardiac death due to ventricular fibrillation. In the latter patient, programmed ventricular stimulation did not induce sustained ventricular tachycardia. All but 2 patients were receiving antiarrhythmic drugs. All patients were on the same drug regimen at the time when both signal-averaged electrocardiograms were obtained. Atrial flutter was accompanied by 2:1 atrioventricular conduction in each patient.

All records had a noise level <0.4 μV. The mean standard (unfiltered) QRS complex duration did not differ before and after conversion to sinus rhythm (97 ± 3 vs 99 ± 2 ms). However, all 3 mean signal-averaged electrocardiographic parameters were significantly different before and after conversion to sinus rhythm. The mean filtered QRS duration (137 ± 13 vs 104 ± 2 ms) and the duration of low-amplitude signals (64 ± 13 vs 30 ± 4 ms) were longer during atrial flutter than during sinus rhythm. Similarly, the mean root-mean-square voltage of the terminal 40 ms of the QRS complex was lower during atrial flutter than during sinus rhythm (17 ± 6 vs 37 ± 5 μV). A late potential was present in 6 of 9 patients during atrial flutter, but in only 1 after conversion to sinus rhythm. Thus, pseudo late potentials were present in 5 of 9 patients during atrial flutter.

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Flutter waves coincided with the terminal portion of the QRS complex in the 5 patients who had pseudo late potentials and in the 1 with a late potential during atrial flutter and sinus rhythm (Figure 1). However, flutter waves were not superimposed on the terminal part of the QRS complex in any of the 3 patients without pseudo late potentials on SAECG (p = 0.01) (Figure 2). In these 3 patients, flutter waves occurred at the onset or within the QRS complex. The ratio of flutter wave duration to the ventricular cycle length was greater in patients with pseudo late potentials (Table I). Flutter wave duration and cycle length, and ventricular cycle length also tended to be longer in patients with pseudo late potentials. These differences did not reach statistical significance, but the number of patients analyzed was limited. The atrioventricular conduction ratio during atrial flutter was not related to the presence of a late potential (2:1 in each patient).

This is the first study to show that atrial flutter affects the accuracy of SAECG. Several other factors including the presence of noncoronary heart disease, bundle branch block or intraventricular conduction delay,

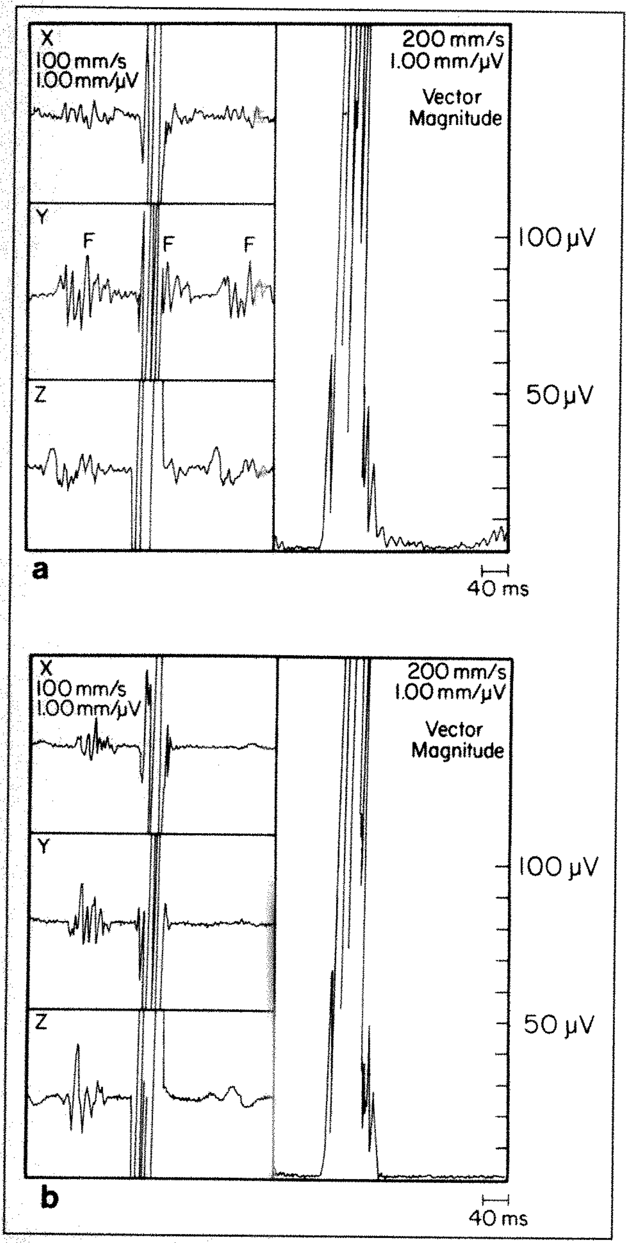

FIGURE 1. Example of signal-averaged electrocardiogram with pseudo late potential during atrial flutter *(a)*, but not during sinus rhythm *(b)*. Second flutter wave (F) occurs at terminal portion of filtered QRS complex simulating late potential (a). Parameters for each signal-averaged electrocardiogram are as follows: standard QRS: *a*, 94 ms, and *b*, 93 ms; filtered QRS: *a*, 164 ms, and *b*, 96 ms; root-mean-square: *a*, 2.7 µV, and *b*, 65.3 µV; and low-amplitude signal duration: *a*, 94 ms, and *b*, 20 ms.

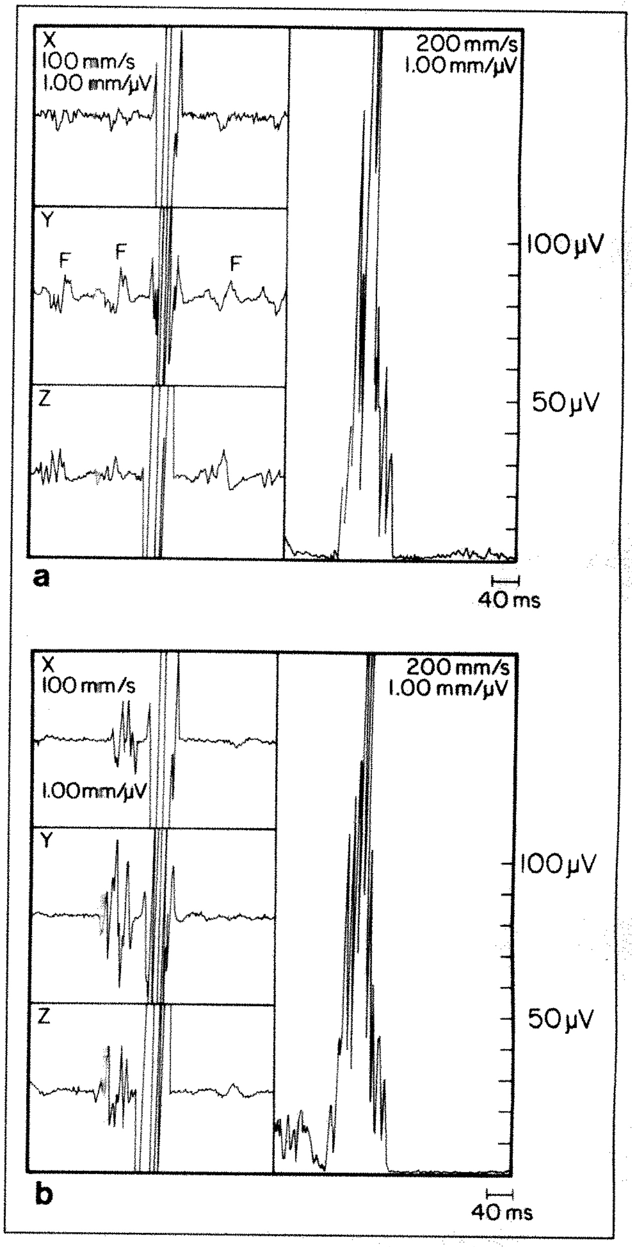

FIGURE 2. Example of signal-averaged electrocardiogram without late potential during atrial flutter *(a)* or sinus rhythm *(b)*. Flutter waves (F) occurred during ventricular activation and did not interfere with terminal portion of QRS complex. Parameters for each signal-averaged electrocardiogram are as follows: standard QRS: *a*, 105 ms, and *b*, 94 ms; filtered QRS: *a*, 86 ms, and *b*, 99 ms; root-mean-square: *a*, 59.4 µV, and *b*, 41 µV; and low-amplitude signal duration: *a*, 16 ms, and *b*, 20 ms.

TABLE I Atrial Flutter Characteristics in Patients With and Without a Late Potential on Signal-Averaged Electrocardiography

	Late Potential	No Late Potential	p Value
Flutter wave CL	239 ± 13 ms	193 ± 13 ms	0.06
Ventricular CL	478 ± 26 ms	387 ± 27 ms	0.06
Flutter wave duration	151 ± 16 ms	100 ± 17 ms	0.06
Ratio of flutter wave duration to ventricular CL	0.35 ± 0.02	0.260 ± 0.007	0.02

CL = cycle length.

and history of cardiac arrest due to ventricular fibrillation have been shown to decrease the predictive accuracy of SAECG.[9,11–14] The timing of the test relative to myocardial infarction affects sensitivity and specificity.[15–18] Electromagnetic or mechanical noise may also decrease the sensitivity and specificity of SAECG.[19]

We hypothesized that atrial flutter waves that coincide with the terminal portion of the QRS complex cause a pseudo late potential on SAECG. In 5 of 9 patients studied, low-amplitude electrical activity at the terminal portion of the QRS complex during atrial flutter was not present during sinus rhythm. In all 5 patients with pseudo late potentials, the timing of the pseudo late potential coincided exactly with that of the atrial flutter wave. Furthermore, in patients without pseudo late potentials during atrial flutter, the flutter waves occurred either at the onset or within the QRS complex. These findings suggest that superimposition of the flutter wave at the terminal portion of the QRS complex was responsible for the pseudo late potential. The ratio of flutter wave duration to ventricular cycle length was greater in patients with pseudo late potentials during atrial flutter, possibly because this increased the probability that a flutter wave would be superimposed on the terminal QRS complex.

This study suggests the possibility that other atrial arrhythmias may affect the diagnostic accuracy of SAECG. However, in a preliminary report, Radin et al[20] showed that atrial fibrillation does not alter signal-averaged electrocardiographic parameters. It remains to be seen if atrial tachycardias affect SAECG.

This study does not exclude the possibility that pseudo late potentials were due to a change in ventricular electrical activation associated with rate, frequency-dependent effects of drugs on the myocardium, or ischemia. The mean ventricular rate was 84 ± 4 beats/min (range 64 to 106) during sinus rhythm compared with 137 ± 7 (range 109 to 167) during atrial flutter. However, 2 recent independent studies showed that SAECG was similar during sinus rhythm and rapid atrial pacing.[21,22] Furthermore, although 1 patient in this study had coronary artery disease, this patient did not report chest pain and did not have ischemic ST-T-wave changes during either atrial flutter or sinus rhythm.

We conclude that atrial flutter may cause a pseudo late potential on SAECG. Thus, SAECG is best not performed to risk-stratify patients for ventricular tachycardia when atrial flutter is present. SAECG is best performed after conversion to sinus rhythm.

REFERENCES

1. Simson MB. Identification of patients with ventricular tachycardia after myocardial infarction from signals in the terminal QRS complex. *Circulation* 1981; 64:235–242.

2. Breithardt G, Becker R, Seipel L, Abenblroth RR. Noninvasive detection of late potentials in man—a new marker for ventricular tachycardia. *Eur Heart J* 1981; 2:1–11.

3. Rozanski JJ, Mortara D, Myerburg RJ, Castellanos A. Body surface detection of delayed depolarization in patients with recurrent ventricular tachycardia and left ventricular aneurysm. *Circulation* 1981;63:1172–1178.

4. El-Sherif N, Gomes JA, Restivo M, Mehra R. Late potentials and arrhythmogenesis. *PACE* 1985;8:440–462.

5. Hombach V, Hopp HW, Kebbel U, Treis I, Osterspey A, Eggeling T, Winter U, Hirche H, Hilger H. Recovery of ventricular late potentials from body surface using the signal averaging and high resolution ECG techniques. *Clin Cardiol* 1986;9:361–368.

6. Simson MB. Signal averaging. *Circulation* 1987;75(suppl III):III-67–III-73.

7. Josephson ME, Horowitz LN, Farshidi A. Continuous local electrical activity. A mechanism of recurrent ventricular tachycardia. *Circulation* 1978;57:659–665.

8. Klein H, Karp RB, Kouchoukos NT, Zorn GL Jr, James TN, Waldo AL. Intraoperative electrophysiologic mapping of the ventricles during sinus rhythm in patients with previous myocardial infarction. Identification of the electrophysiologic substrate of ventricular arrhythmias. *Circulation* 1982;66:847–853.

9. Simson MB, Untereker WJ, Spielman SR, Horowitz LN, Marcus NH, Falcone RA, Harken AH, Josephson ME. Relation between late potentials on the body surface and directly recorded fragmented electrograms in patients with ventricular tachycardia. *Am J Cardiol* 1983;51:105–112.

10. Untereker WJ, Spielman SR, Waxman HL, Horowitz LN, Josephson ME. Abnormalities with recurrent sustained tachycardia and a history of myocardial infarction. *Am J Cardiol* 1985;55:974–979.

11. Borbola J, Ezri MD, Demes P. Correlation between the signal averaged electrocardiogram and electrophysiologic study findings in patients with coronary artery disease and sustained ventricular tachycardia. *Am Heart J* 1988;115:816–824.

12. Nalos PC, Gang ES, Mandel WJ, Ladenheim ML, Lass Y, Peter T. The signal-averaged electrocardiogram as a screening test for inducibility of sustained ventricular tachycardia in high risk patients: a prospective study. *J Am Coll Cardiol* 1987;9:539–548.

13. Freedman RA, Gillis AM, Keren A, Soderholm-Difatte V, Mason JW. Signal averaged electrocardiographic late potentials in patients with ventricular fibrillation or ventricular tachycardia: correlation with clinical arrhythmia and electrophysiologic study. *Am J Cardiol* 1985;55:1350–1353.

14. Simson MB, Falcone R, Dresden C, Buxton A, Marchlinski F, Waxman H, Josephson M. The signal averaged ECG and electrophysiologic studies in patients with ventricular tachycardias and fibrillation (abstr). *Circulation* 1983;68:III–173.

15. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: natural history and prognostic significance. *Circulation* 1986; 74:1280–1289.

16. Verzoni A, Romano S, Pozzoni L, Tarricone D, Sangiorgio S, Groce L. Prognostic significance and evolution of late ventricular potentials in the first year after myocardial infarction: a prospective study. *PACE* 1989;12:41–51.

17. El-Sherif N, Ursell SN, Bekheit S, Fontaine J, Turitto G, Henkin R, Caref EB. Prognostic significance of the signal averaged ECG depends on the time of recording in the post infarction period. *Am Heart J* 1989;118:256–264.

18. Gomes J, Mehra R, Hariman R, Barreca P, El-Sherif N. A prospective study of the high frequency components of the terminal portion of the QRS in acute myocardial infarction (abstr). *Circulation* 1983;68(suppl III):III-172.

19. Steinberg JS, Bigger JT. Importance of the endpoints of noise reduction in analysis of the signal averaged electrocardiogram. *Am J Cardiol* 1989;63:556–560.

20. Radin MM, Volgman AS, Jhangiani A, Uretz EF, Parrillo JE, Buckingham TA. Does atrial fibrillation cause false positive late potentials? (abstr). *Circulation* 1991;84:II-596.

21. Greenspon A, Volosin K. The effects of atrial pacing on the signal averaged electrocardiogram in patients with coronary artery disease. *Am Heart J* 1990; 119:29–34.

22. Kremers MS, Black WH, Lange R, Wells PJ, Solo M. Electrocardiographic signal averaging during atrial pacing and effect of cycle length on the terminal QRS in patients with and without inducible ventricular tachycardia. *Am J Cardiol* 1990; 66:1095–1098.

Signal-Averaged Electrocardiography in Asymptomatic Alcoholics

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Ventricular late potentials (i.e., low-amplitude, high-frequency waveforms and altered frequency components in the terminal QRS complex) can be detected by signal-averaged surface electrocardiography. Their presence usually indicates areas of fibrous scar tissue in the myocardium, with delayed and fragmented impulse conduction through the border zones surrounding these areas. Signal-averaged electrocardiography has been successfully used in assessing the risk of ventricular arrhythmias and sudden arrhythmic death after myocardial infarction.[1] Sudden cardiac death is also relatively frequent among alcoholics, and life-threatening ventricular arrhythmias are found in alcoholics without heart disease.[2] Earlier electrophysiologic studies have shown that patients with alcoholic cardiomyopathy can have localized delays in intraventricular conduction, suggesting nonuniform myocardial involvement.[3] To find out whether alcoholics without clinically evident heart disease have intraventricular conduction abnormalities identifiable as ventricular late potentials, we recorded signal-averaged electrocardiograms in a group of male and female alcoholics.

We studied 39 alcoholics (25 men and 14 women, mean age 41 years, range 23 to 61) who entered our hospital for detoxification and research purposes. Most patients were episodic drinkers. The mean duration of their heavy drinking was 14 years (0.5 to 30), the last uninterrupted drinking period averaged 21 weeks (0.4 to 250), and the mean amount of alcohol consumed daily during this period was 247 g (70 to 600). No patient had been hospitalized for cardiac arrhythmias or was receiving antiarrhythmic drugs. Their mean systolic and diastolic blood pressures were 134 ± 20 and 91 ± 15 mm Hg, respectively. On admission, red cell mean corpuscular volume averaged 96 fl (86 to 15), aspartate aminotransferase 100 U/liter (19 to 293) and gammaglutamyltranspeptidase 321 U/liter (15 to 1,510). The healthy control group comprised 14 men and 14 women (mean age 39 years, range 26 to 50), many of whom were members of the hospital staff. Their alcohol use was modest. The systolic and diastolic blood pressures of the control group were 132 ± 12 and 84 ± 7 mm Hg, respectively. No subject studied had bundle branch block in a 12-lead electrocardiographic recording. Signal-averaged electrocardiograms were recorded in a warm, quiet, copper-insulated room using a commercially available recorder (Mac 12, Marquette Electronics, Milwaukee, Wisconsin). A bidirectional 40 to 250 Hz band-pass filter was used. The electrodes were placed in orthogonal X, Y and Z positions after mildly abrading and carefully cleansing the skin. The onset and offset of QRS complex were automatically determined by the recorder. Recordings were visually inspected later. The duration of the filtered QRS complex (QRSf), the root-mean-square voltage (RMSV) of the terminal 40 ms of the filtered QRS, and the duration of the QRSf $<40\ \mu$V (LAS) were determined. Signal-averaged electrocardiography was performed in all 39 alcoholics on admission, and in 32 also after a mean period of 12 days (7 to 14) of abstinence. In 9 control subjects, recordings were repeated after an average of 21 days (7 to 46) to assess the repeatability of the measurements. Echocardiographic imaging of the left ventricle was performed in the alcoholics with cross-sectional scanners (Toshiba SSH-60A and SSH 160A, and Aloka 830), and the left ventricular mass was calculated as previously described.[4] Student's t *and Fisher's exact tests were used in the statistical evaluation.*

The mean number of beats averaged was 221 (101 to 261) in the alcoholics and 248 (106 to 258) in the control subjects, and the noise levels were 0.45 ± 0.23 and 0.32 ± 0.22 μV, respectively. Table I shows the signal-averaged electrocardiographic data in alcoholics and control subjects separately for both sexes; the only significant difference between female and male alcoholics and control subjects was the longer QRSf in controls ($p = 0.03$ for men, and $p = 0.01$ for women). The repeated recordings in alcoholics after detoxification did not differ significantly from those obtained on admission (data not shown). The results of the 2 measurements in the 9 healthy control subjects showed good agreement; SDs of the differences in QRSf, RMSV and LAS were 1.8 ms, 6.4 μV and 2.3 ms, respectively. Using standard criteria for normalcy,[1] only 1 alcoholic had abnormal results in all 3 parameters, as compared with no control subjects. Three alcoholics (8%) and 7 control subjects (25%) had QRSf >14 ms ($p = 0.08$). No alcoholic had detectable left ventricular failure. The median left ventricular mass normalized to body surface area was 80 g/m^2 (48 to 17). QRSf was 101 ± 5 ms in patients with left ventricular mass index less than median, and 105 ± 8 ms in those with mass index greater than median ($p = 0.08$); there were no statistically significant differences in RMSV or LAS between these groups.

This study shows that chronic alcoholics without detectable heart disease do not have ventricular late potentials in signal-averaged electrocardiography either immediately after a heavy drinking period or during abstinence. Furthermore, the results are similar to those obtained in a healthy control group of the same age. Chronic heavy alcohol consumption increases left ventricular mass and may cause subclinical impairment in left ventricular function.[3] Although previous work has shown that the duration of QRSf is positively correlated with left ventricular mass,[5] we found no difference

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TABLE I Signal-Averaged Electrocardiographic Data in Alcoholics on Admission and in Healthy Control Subjects

	Alcoholics		Control Subjects	
Parameter	Men (n = 25)	Women (n = 14)	Men (n = 14)	Women (n = 14)
Filtered QRS (ms)	103 ± 8	100 ± 5	111 ± 10	104 ± 6
RMSV40 (μV)	56 ± 24	53 ± 18	45 ± 26	49 ± 21
LAS40 (ms)	27 ± 8	29 ± 5	29 ± 9	28 ± 8

Values are mean ± SD. Filtered QRS was significantly longer in male ($p = 0.01$) and female ($p = 0.03$) control subjects than in male and female alcoholics.

LAS40 = duration of signals <40 uV in terminal 40 ms of filtered QRS; RMSV40 = root-mean-square voltage of terminal 40 ms of filtered QRS.

in the duration of QRSf between alcoholics with left ventricular mass index greater or less than the median. Furthermore, when QRSf was analyzed separately for both sexes, it was shorter in both male and female alcoholics than in control subjects (Table I). The low frequency of ventricular late potentials in the alcoholics of this study does not exclude nonuniformity of alcohol-induced changes in myocardium. The location or extent of the slow-conducting myocardial areas can be such that the signs of delayed conduction are hidden within the QRS complex. The results are at variance with those of Ettinger et al[6] who found prolonged QRS duration with high-speed electrocardiography in patients with alcohol-related cardiac arrhythmias. The disparity can be explained by the differences in study cohorts; none of our patients was hospitalized because of cardiac arrhythmias, and none had experienced serious arrhythmias in the past. In conclusion, ventricular arrhythmia substrate as measured by signal-averaged electrocardiography parameters was not detected in alcoholics without clinically evident heart disease.

REFERENCES

1. Breithardt G, Cain ME, El-Sherif N, Flowers NC, Hombach V, Janse M, Simson MB, Steinbeck G. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography: a statement by task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol* 1991;17:999–1006.

2. Moushmoush B, Abi-Mansour P. Alcohol and the heart. The long-term effects of alcohol on the cardiovascular system. *Arch Intern Med* 1991;151:36–42.

3. Luca C. Electrophysiological properties of right heart and atrioventricular conducting system in patients with alcoholic cardiomyopathy. *Br Heart J* 1979;42:274–281.

4. Kupari M, Koskinen P, Suokas A. Left ventricular size, mass and function in relation to the duration and quantity of heavy drinking in alcoholics. *Am J Cardiol* 1991;67:274–279.

5. Raineri AA, Traina M, Lombardo RMR, Rotolo A. Relation between late potentials and echocardiographically determined left ventricular mass in healthy subjects. *Am J Cardiol* 1991;67:425–427.

6. Ettinger PO, Wu CF, De La Cruz C Jr, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978;95:555–562.

Balloon Angioplasty of Aortic Recoarctation

I read with interest the paper by Anjos et al[1] published in a recent issue of *The American Journal of Cardiology.* There are limited data published with regard to balloon angioplasty of aortic recoarctation, and some of the important published contributions[2–4] have not been reviewed by the authors. However, this paper brings out several important issues that are worthy of further discussion and clarification.

Criteria for success: Although it is true that different criteria such as percent reduction of gradient and percent increase in coarcted segment diameter have been used for evaluation of success in different studies, a residual gradient of ≤20 mm Hg has also been used by several workers. As a matter of fact, we have been able to tabulate[4,5] the rates of residual or recoarctation reported by most workers based on residual peak-to-peak gradient in excess of 20 mm Hg both for the immediate and follow-up results. The additional use of achieving normal blood pressure and lack of major damage to the aortic wall as suggested by Anjos et al[1] are also useful adjuncts in defining success of the procedure.

Poor results: In the series reported by Anjos et al[1] immediate success, defined as reduction in gradient to ≤20 mm Hg, occurred in only 17 of 26 patients (65%). At a mean follow-up of 1.8 years, 11 patients (42%) had a poor result, again defined as gradients >20 mm Hg. Our reported experience,[4,5] though limited to 10 patients, was far more rewarding than that reported by Anjos. The peak-to-peak systolic pressure gradients were reduced from 52 ± 21 mm Hg to 15 ± 7 mm Hg after balloon angioplasty, with only 2 (20%) patients having residual gradients in excess of 20 mm Hg. At a mean follow-up of 1.3 years (not too different from 1.8-year mean follow-up of Anjos et al[1]), the gradients decreased further to 6 ± 6 mm Hg. The residual gradients ranged between 0 and 18 mm Hg and *none* had gradients in excess of 20 mm Hg. No patient developed aneurysms. The results from both studies are listed in Table I. The age of balloon angioplasty, interval between surgery and balloon angioplasty and type of surgery (Table I) are not significantly different from each other. It appears that the technique of balloon angioplasty used is different. Anjos et al[1] used balloon sizes similar to aortic diameter proximal coarctation early in their series. Later they used balloons similar to the aortic diameter at the level of the diaphragm. I believe that balloon size is important in not only providing adequate relief of aortic obstruction, but also in preventing aortic rupture[6,7] and immediate or late formation of aneurysms.[8–10] The balloon diameter used for dilatation should be 2 or more times the size of the coarcted segment[11] but no larger than the descending aorta at the level of the diaphragm.[5,12,13] In practice, we select a balloon size that is midway between the diameter of the aortic isthmus or transverse aortic arch (aortic

TABLE I Comparison of Recoarctation Balloon Angioplasty Data

	Anjos et al[1]	Rao and Chopra[5]
No. of children undergoing BA	26	10
Age (mos) at angioplasty, mean ± SD (range)	* (3-220)	29 ± 25 (6-84)
Interval (mos) between surgery and angioplasty, mean ± SD (range)	* (2-216)	26 ± 26 (6-3,484)
Type of surgery	EE-4 SF-17 PA-5	EE-5 SF-2 PA-2 IA-1
Peak gradient (mm Hg), mean ± SD		
Before BA	49 ± 17	52 ± 21
After BA	20 ± 17	15 ± 7
No. of pts. with gradients >20 mm Hg (%)	9 (35)	2 (20)
Duration of follow-up (mos), mean ± SD	22 ± 22	16 ± 7
Gradient at follow-up (mm Hg), mean ± SD	Not given	6 ± 6
No. of pts. with gradients >20 mm Hg (%)	11 (42)	0 (0)
Aneurysms–no. (%)	2 (8)	0 (0)

*Mean and SD not given.
BA = balloon angioplasty; EE = resection with end-to-end anastomosis; IA = repair of interrupted aortic arch; PA = patch angioplasty; SF = subclavian flap angioplasty.

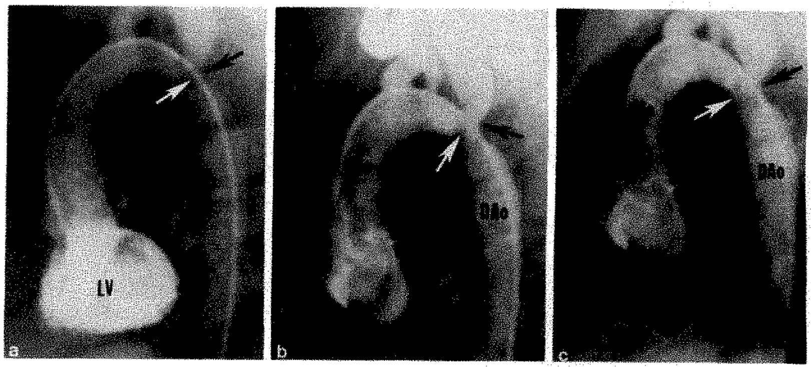

FIGURE 1. Lateral cineangiographic views of the aorta (Ao) showing aortic coarctation *(arrows)*, which is severe before balloon angioplasty *(a)* (Table II, case 3). This improved after balloon dilatation with an 8 mm balloon *(b)* but is still narrowed with a residual peak systolic pressure gradient of 20 mm Hg. Repeat balloon angioplasty with a 10 mm balloon resulted in a wide open coarcted segment *(c)* with reduction of pressure gradient to 14 mm Hg. DAo = descending aorta; LV = left ventricle.

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TABLE II Effect of Balloon Size on Immediate Response of the Pressure Gradient Across the Coarctation After Balloon Angioplasty

Case No.	Age (yr) & Sex	Status— Balloon Size	AAo (mm Hg)	DAo (mm Hg)	Gradient (mm Hg)
1	5 F	Pre	118	87	31
		10 mm	111	87	24
		12 mm	109	99	10
2	10 F	Pre	137	79	58
		10 mm	125	90	35
		12 mm	130	113	17
3	2 F	Pre	133	103	30
		8 mm	96	76	20
		10 mm	90	76	14
4	1.5 M	Pre	103	72	31
		8 mm	106	71	35
		10 mm	96	79	17

AAo = ascending aorta; DAo = descending aorta; Pre = before balloon angioplasty.

segments proximal to coarctation site) and the diameter of the descending aorta at the level of diaphragm. If there is no adequate relief of obstruction (Figure 1, Table II), a balloon as large as the descending aorta at the level of the diaphragm is chosen for dilatation.[14,15] The objective is to apply "controlled" injury with radial forces of a balloon; this should be sufficiently large to produce relief of obstruction, but not large enough to produce aortic rupture and/or aneurysms. For some reason, descending aortic size at the level of diaphragm appears to be most appropriate for selecting balloon size for angioplasty. Meticulous attention to the details of the technique and balloon size are necessary to prevent complications and achieve a good result.

Causes of poor result: The analysis of Anjos et al of factors influencing late results are very helpful to the reader. They identified the small aortic arch diameter (proximal to coarct segment) as a predictor of poor late hemodynamic result. A similar examination of factors responsible for restenosis following balloon angioplasty of native coarctation by our group[16] also identified hypoplasia of aortic segments proximal to the coarctation site as a cause of restenosis. Thus, the data for both native and recoarctations are consistent with regard to this aspect. Although this is true, it should be realized that adequate relief of obstruction encourages greater flow across the aortic segments, causing their growth as demonstrated by aortic remodeling studies performed by us[17] and others.[18,19] This also explains why some patients in Anjos' study improved despite arch hypoplasia. Therefore, we agree with Anjos et al that balloon dilatation should be attempted even with unfavorable arch anatomy but suggest that adequate-sized balloons be used.

Anjos et al[1] also recognized that the use of balloons smaller than the descending aortic diameter is associated with poor late hemodynamic result. The role of and use of adequate-sized balloons has already been discussed in the earlier section.

Conclusion: Although the study by Anjos et al ignored some of the earlier works on balloon angioplasty of aortic recoarctation and used inadequate balloon sizes in the early part of their study, it has made important contributions by focusing our attention to the definition of successful balloon angioplasty and to identification of the causes of a poor result. Their study gave me impetus to review the method of selecting a balloon size that is likely to produce successful balloon angioplasty of aortic recoarctation.

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REFERENCES

1. Anjos R, Qureshi SA, Rosenthal E, Murdoch I, Hayes A, Parsons J, Baker EJ, Tynan M. Determinants of hemodynamic results of balloon dilatation of aortic recoarctation. *Am J Cardiol* 1992;69:665–671.

2. Lababidi ZA, Daskalopoulos DA, Stoeckle H Jr. Transluminal balloon coarctation angioplasty: experience with 27 patients. *Am J Cardiol* 1984;54: 1288-1291.

3. Allen HD, Marx GR, Ovitt TW, Goldberg SJ. Balloon dilatation angioplasty for coarctation of the aorta. *Am J Cardiol* 1986;57:828–832.

4. Rao PS, Wilson AD, Chopra SP. Immediate and follow-up results of balloon angioplasty of postoperative recoarctation in infants and children. *Am Heart J* 1990;120:1315–1320.

5. Rao PS, Chopra PS. Role of balloon angioplasty in the treatment of aortic coarctation. *Ann Thorac Surgery* 1991;52:621–631.

6. Balaji S, Oommen R, Rees PG. Fatal aortic rupture during balloon dilatation of recoarctation. *Br Heart J* 1991;65:100–101.

7. Rao PS. Fatal aortic rupture during balloon dilatation of recoarctation (letter). *Br Heart J* 66:406–407.

8. Joyce DH, McGrath LB. Pseudoaneurysm formation following balloon angioplasty for recurrent coarctation of the aorta. *Cathet Cardiovasc Diagn* 1990; 20:133–135.

9. Rao PS. Pseudoaneurysm following balloon angioplasty (letter). *Cathet Cardiovasc Diagn* 1991;23: 150–153.

10. Saul JP, Keane JF, Fellows KE, Lock JE. Balloon dilatation angioplasty of postoperative aortic obstructions. *Am J Cardiol* 1987;59:943–948.

11. Lock JE, Bass JL, Amplatz K, Fuhrman BP, Castaneda-Zuniga W. Balloon dilation angioplasty of aortic coarctations in infants and children. *Circulation* 1983;68:109–116.

12. Rao PS. Balloon angioplasty for coarctation of the aorta in infancy. *J Pediatr* 1987;110:713–718.

13. Rao PS, Najjar HN, Mardini MK, Solymar L, Thapar MK. Balloon angioplasty for coarctation of the aorta: immediate and long-term results. *Am Heart J* 1988;13:109–115.

14. Rao PS. Balloon angioplasty of native aortic coarctation (letter). *J Am Coll Cardiol*, in press.

15. Rao PS. Balloon angioplasty for aortic recoarctation following previous surgery. In: Rao PS, ed., Transcatheter Therapy in Pediatric Cardiology. New York: Wiley-Liss, Inc., in press.

16. Rao PS, Thapar MK, Kutayli F, Carey P. Causes of recoarctation after balloon angioplasty of unoperated aortic coarctation. *J Am Coll Cardiol* 1989;13: 109–115.

17. Rao PS, Carey P. Remodeling of the aorta following successful balloon coarctation angioplasty. *J Am Coll Cardiol* 1989;14:1312–1317.

18. Beekman RH, Rocchini AP, Dick M II, Snider AR, Crowley DC, Serwer GA, Spicer RL, Rosenthal A. Percutaneous balloon angioplasty for native coarctation of the aorta. *J Am Coll Cardiol* 1987;10: 1078–1084.

19. Suarez de Lezo J, Sancho M, Pan M, Romero M, Olivera C, LuQue M. Angiographic follow-up after balloon angioplasty for coarctation of the aorta. *J Am Coll Cardiol* 1989;13:689–695.

Relation of Site of Acute Myocardial Infarction to the Site of Maximal Coronary Narrowing

Giroud et al[1] in their article, "Relation of the Site of Acute Myocardial Infarction to the Most Severe Coronary Arterial Stenosis at Prior Angiography," raise the question of whether the site of acute myocardial infarction (AMI) can be predicted from a previous coronary angiogram. They conclude that "AMI occurs in relation to the previously most stenotic lesion only in approximately one-third of cases." We submit that this finding is more likely due to study design than the biology of coronary lesions.

Several studies involving over 25,000 patients have shown clearly that mortality rates of patients with coronary artery disease (CAD) are directly proportional to the number of diseased coronary vessels, the extent of the angiographic stenoses, and the degree of left ventricular dysfunction.[2–5] Giroud and his colleagues, however, make no reference to mortality as a selective factor in the makeup of their case series. They introduce a serious bias into their study group by selecting only patients who survived long enough to have an intervening AMI and a second coronary angiogram. Their case series represents a more robust, less diseased, survival group, rather than all CAD patients including severely diseased patients who die before having a second angiogram. Focusing only on those CAD patients who survive long enough to have an AMI and a second coronary angiogram introduces a selection bias that precludes an answer to their original question.

They raise and appear to answer an important generic question by providing data, as they rightfully indicate, on a selected group of patients. There is a discordance between the generic question of whether the site of AMI can be predicted from a previous coronary angiogram and their answer derived from a highly selected population. Readers might easily infer from this article that most CAD patients who experience an AMI do so because of an event in one of their lesser narrowed arteries. Their data do not permit this conclusion.

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REFERENCES

1. Giroud D, Li JM, Urban P, Meier B, Rutishauser W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol* 1992;69:729–732.

2. Ringqvist I, Fisher LD, Mock M, Davis KB, Wedel H, Chaitman BR, Passamani E, Russell RO Jr, Alderman EL, Kouchokas NT, Kaiser GC, Ryan TJ, Killip T, Fray D. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest* 1983;71:1854–1866.

3. Friesinger GC, Page EE, Ross RS. Prognostic significance of coronary arteriography. *Trans Assoc Am Physicians* 1970;83:78–92.

4. Bruschke AV, Proudfit WL, Sones FM Jr. Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. II. Ventriculographic and other correlations. *Circulation* 1973;47:1154–1163.

5. Burggraf GW, Parker JO. Prognosis in coronary artery disease. Angiographic, hemodynamic, and clinical factors. *Circulation* 1975;51:146–156.

Thrombolytic Therapy After Cardiopulmonary Resuscitation in Acute Myocardial Infarction

Scholz et al[1] are to be commended for their important article regarding complications (or lack thereof) of cardiopulmonary resuscitation (CPR) and thrombolytic therapy in acute myocardial infarction (AMI). As we previously noted in a case report,[2] thrombolytic therapy can be given successfully after prolonged CPR in AMI.

Scholz concludes that, "There was no difference in the rate of bleeding complications for patients with $(n = 43)$ and without $(n = 547)$ resuscitation (18.6 vs 16.1%; chi-square = 0.34, p = not significant)." However, only 16 of their 43 patients received thrombolytic therapy after successful CPR. The remaining 27 patients had thrombolytic therapy first, then developed cardiac arrest requiring CPR or had thrombolytic therapy administered during ongoing CPR in "nearly hopeless clinical situations." Furthermore, of these 16 patients who received thrombolytic therapy after successful CPR, only 4 received intravenous thrombolysis as the sole route of administration (10 received only intracoronary thrombolysis and 2 received both intracoronary and intravenous thrombolysis). Since most patients with AMI present to institutions without invasive cardiac catheterization facilities, the intravenous route in this situation would of necessity be utilized. The real issue facing most clinicians is whether to administer intravenous thrombolytic therapy after successful CPR, a question that cannot be resolved by only 4 patients in this category in Scholz's review.

Tenaglia et al[3] have already shown no additional complications attributable to thrombolytic therapy in patients receiving short term (<10 minutes) CPR in AMI. However, whether this conclusion can be extended to patients receiving intravenous thrombolytic therapy following prolonged (>10 minutes) CPR in AMI must await more data.

Certainly the preliminary data are encouraging, and we continue to agree that in the absence of gross trauma from CPR, thrombolytic therapy in AMI should not necessarily be excluded because of prolonged duration of resuscitation.

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REFERENCES

1. Scholz KH, Tebbe U, Herrmann C, Wojcik J, Lingen R, Chemnitius JM, Brune S, Kreuzer H. Frequency of complications of cardiopulmonary resuscitation after thrombolysis during acute myocardial infarction. *Am J Cardiol* 1992;69:724–728.

2. Neches RB, Goldfarb AM, Saviano GJ. Thrombolytic therapy in acute myocardial infarction following prolonged cardiopulmonary resuscitation. *Clin Cardiol* 1991;14:616–619.

3. Tenaglia AN, Califf RM, Candela RJ, Kereiakes DJ, Berrios E, Young SY, Stack RS, Topol EJ. Thrombolytic therapy in patients requiring cardiopulmonary resuscitation. *Am J Cardiol* 1991;68:1015–1019.

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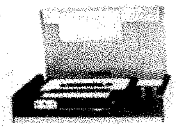

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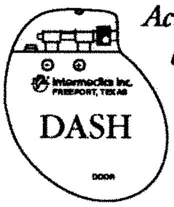

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Fax CV to 816-444-7585,or send to:
ROCKHILL CARDIOLOGY GROUP, INC.
Rockhill Medical Plaza North,
6650 Troost Ave. • Suite 106
Kansas City, MO 64131

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KNOXVILLE, TENNESSEE CARDIOLOGIST

CARDIOLOGIST - Four FACC's with diverse subspecialty interests seek a fifth Cardiologist to join a JCAH hospital-based practice in attractive Knoxville, Tennessee (population 300K+). The ideal candidate will be US trained and able to add skills to a group that is currently practicing EP studies, pacemaker and cardioverter implantation, angioplasty, echo, and newer interventional techniques. Value oriented medicine and family time are very important to this group. Competitive compensation and benefits package with partnership opportunity. For more information on a confidential basis, please contact:

Gerry Chapman
ST. MARY'S MEDICAL CENTER
900 E. Oak Hill Avenue, Knoxville, TN 37917
CV or call collect 615-971-6758

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CARDIOLOGIST

Immediate opening for invasive or noninvasive BC/BE cardiologist in Southwestern Colorado. State-of-the-art nonivasiive lab including SPECT-nuclear, TEE/echo. Early partnership possible. Mountain setting with close proximity to the desert and Canyonlands. Skiing, biking, hiking, fishing, arts, college, Indian ruins, tourism. CV to:

P.O. Box 2123 • Durango,CO 81302
(303) 247-1120

CALIFORNIA (Northern)

Non-Invasive/Invasive. Associate with 3 cardiologists in lake/resort area 2 ½ hrs. north of San Francisco.

Call Anders Karlman
(800) 634-3561

ALABAMA CARDIOLOGIST

Immediate opportunity for BC/BE in cardiovascular disease to join a 4-physician invasive and clinical cardiology group in a large southeastern city. Reply to:

SOUTHERN CARDIOLOGY, P.C.
2022 Brookwood Medical Center
Drive Suite 510
Birmingham, Alabama 35209

FLORIDA INVASIVE/NON-INVASIVE CARDIOLOGIST

Excellent opportunities available for BC/BE cardiologists to join successful, well-established private practices. Ideally situated in affluent and rapidly growing communities surrounding beautiful Ft. Lauderdale. Salary, incentives and excellent benefit package. Partnership opportunities. Send CV to:

NORTH BROWARD HOSPITAL DISTRICT
Physician Recruitment
303 S.E. 17th Street • Ft. Lauderdale, FL 33316

CENTRAL MINNESOTA HEART CENTER

Cardiologist, BC/BE, desired for consultative practice in delightful Minnesota community of 90,000 with referral base of 250,000. Personable, energetic person desired as sixth cardiologist in a 31-person Internal Medicine/Internal Medicine Subspecialty Clinic. Community has three colleges, excellent school system and abundant recreational activities. Rare opportunity to practice high-quality cardiology in a beautiful environment with excellent financial compensation and lifestyle benefits. Please contact:

John Mahowald, M.D. (or)
Mark J. Murphy, Administrator
THE ST. CLOUD CLINIC
OF INTERNAL MEDICINE, LTD.
1200 Sixth Avenue North
St. Cloud, MN 56303
(612) 252-5131

SALEM, OREGON INVASIVE CARDIOLOGIST

Opportunity immediately available for BC/BE invasive cardiologist. To join cardiologist in private practice in Salem, OR. Send CV to:

J. Devorss, M.D.
1050 Oak St. SE
Salem, OR 97301
(503) 362-4146

LAKE MICHIGAN CARDIOLOGIST

Position available for Board Certified/Board Eligible Cardiologist to join a non-invasive cardiologist in a 50+ physician multi-specialty Clinic. Located on lake Michigan one hour north of Milwaukee in city of 50,000 with drawing area of 100,000+. Excellent benefit package including relocation expenses. Contact:

James Gularek, Administrator
THE SHEBOYGAN CLINIC
2414 Kohler Memorial Drive
Sheboygan, WI 53081
414-457-4461

WEST

Position available-Beginning July 1, 1993. Recruiting for a non-invasive Cardiologist. Santa Cruz Medical Clinic is a multi-specialty group located on Monterey Bay, 90 miles south of San Francisco. Send CV to:

President/CEO
2025 Soquel Ave.
Santa Cruz, CA 95060

FLORIDA

Very busy BC non-invasive cardiologist is seeking a BC/BE invasive/non-invasive cardiologist to begin immediately. The practice is located in Winter Haven, Florida. A rapidly growing community midway between Tampa and Orlando. The community supports a 600 bed hospital with a full array of cardiology services.

Please send replies to:

WINTER HAVEN CARDIOLOGY
350 First St. North
Winter Haven, Florida 33881

Dean
Medical Center

CARDIOLOGIST WITH NUCLEAR CARDIOLOGY TRAINING

Dean Medical Center, a 220 physician multispecialty group located in Madison, Wisconsin, is actively seeking a BE/BC Clinical Cardiologist/Nuclear Cardiologist to join its 7 member Cardiology Department. Ideal candidate should have excellent clinical cardiology and nuclear cardiology skills. Practice would be a mix of nuclear cardiology and clinical cardiology with cardiac catheterization interest optional.

Madison is the state capital of Wisconsin with a metro area of over 300,000 and the home of the University of Wisconsin with enrollment of over 45,000 students. Excellent compensation and benefits provided with full time employment leading to shareholder status in 2 years. For more information contact:Scott M. Lindblom **DEAN MEDICAL CENTER** 1313 Fish Hatchery Road, Madison, Wisconsin work: (608) 259-5151 or home: (608) 276-8989

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DALLAS, TX CARDIOLOGIST

Expanding, successful, 10 person cardiology practice seeks invasive/non-invasive cardiologists for outstanding opportunities at desirable suburban Dallas hospitals. Attractive salary/benefits package. Join the Southwest's premier cardiology group.

Texas Cardiology Consultants

Reply with CV to: Practice Manager
712 N. Washington, #300
Dallas, TX 75246
FAX (214) 824-4943

UPPER MIDWEST CARDIOLOGIST

Invasive, Noninvasive or EP - to join busy CD group in Upper Midwest city of 700,000. Excellent diagnostic facilities, great lifestyle location with strong economy. Opportunity for academic appointment and teaching. Excellent compensation with salary plus production bonus first year. Send CV to Greg Peterson.

THE PETERSON GROUP, INC.
8700 Monrovia • Suite 208
Shawnee Mission, KS 66215
Tel: 800-669-4804
Fax: 913-599-6776

VIRGINIA

Invasive or Non-Invasive Cardiologist sought for practice opportunity in coastal Virginia town just 30 minutes from the Chesapeake Bay. Modern, financially-strong hospital. Generous guarantee. Call schedule caters to family life. Equestrian interests run high in this community, and other recreational activities include water sports and tackling premier golf courses. This family-oriented community offers excellent schools and easy drives to Richmond and Washington, D.C. Forward Vitae or call:

Susan Bloom
Dept. B, P.O. Box 2816
Durham, NC 27715
800-477-0600

Need More Classified Information?

Call Marc Rentzer
212-463-6487
800-344-7775

WATERFRONT, LONG/ISLAND CARDIOLOGIST

Waterfront community, Long Island, NY. Exceptional opportunity to join a dynamic expanding 26-physician multispecialty group. Brand new facility. Seeking cardiologist BE/BC. Progressive incentive salary leading to full partnership three years. Position Available now.

Send CV to Box 1285
The American Journal of Cardiology
249 West 17th Street • NY, NY 10011

NORTH CAROLINA•SOUTH CAROLINA VIRGINIA•KENTUCKY•TENNESSEE GEORGIA•OHIO•PENNSYLVANIA NEW JERSEY

Invasive and Non-Invasive Cardiologists sought for numerous practice opportunities. Many offering lucrative financial packages. Locations include cities, small towns, mountain sites, coastal areas. Possible academic affiliations. Forward vitae or call:

Susan Bloom
AM CARE PHYSICIAN SEARCH
Dept. B, P.O. Box 2816, Durham, NC 27715
800-477-0600

CARDIOLOGY

Nine member Cardiology group practice in southeast university city seeks BE/BC Cardiologists for the following positions:

A. Electrophysiologist to direct full-service EP program in dedicated lab.
B. Clinical Cardiologist with special interest in lipid management and/or cardiac rehabilitation.
C. Clinical Cardiologist with interest in a non-interventional practice (duties may include diagnostic catheterization).
D. Clinical cardiologist to expand a growing practice at an associated hospital within thirty miles.

All positions offer competitive salary, early partnership, and excellent benefits package.

Send curriculum vitae to:
FORT SANDERS HEALTH SYSTEMS
Linda Porter-Tillman, R.N.
Director of Practice Development
280 Fort Sanders West Boulevard • Suite 214
Knoxville, TN 37922
(615) 531-5007

TM

Pediatric Cardiologist

Dartmouth-Hitchcock Medical Center seeks full-time pediatric cardiologist in Lebanon to join active, growing regional 5-person joint DHMC-University of Vermont pediatric cardiology program.

- Well-established patient population
- Extensive outreach program
- Extensive echocardiography caseload
- Active cardiac catheterization program
- Academic commitments include research and teaching of students, residents and adult cardiology fellows
- Association with existing active regional perinatal and pediatric intensive care programs
- Opportunity to expand pediatric electrophysiology

Submit CV to: Michael Flanagan, MD, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756. (603) 650-8658. Equal opportunity/affirmative action employer.

Dartmouth-Hitchcock Medical Center
The Hitchcock Clinic
Lebanon, New Hampshire

Valley Diagnostic Medical & Surgical Clinic, P.A.

CARDIOLOGIST

Move into established practice in Multispecialty Clinic

Position requires expertise in invasive/ non-invasive procedures. Cardiology team includes CV/Thoracic surgeon. Competitive guaranteed salary with bonus incentive plan, malpractice insurance, relocation expense and interview expense included in benefits package. Enjoy a sub-tropical climate on the Texas Gulf Coast. Location is attractive to those who enjoy outdoor sports such as fishing, golf, and sailing. Look into joining our great team.

CONTACT: Mark Rowe
Valley Diagnostic Medical & Surgical Clinic, P.A.
2200 Haine Dr., Harlington, TX 78550, 1-800-852-4543
In Texas 1-800-338-4590 or 512-421-5199

#1 In Healthcare Recruitment

MILWAUKEE AREA

Cardiologist BC/BE for invasive and non-invasive practice to join the staff of a 68 physician multi-specialty clinic located in suburban Milwaukee. Excellent salary and fringe benefits. Submit CV to:

Administrator
P.O. Box 427
Menomonee Falls, WI 53051

INVASIVE CARDIOLOGIST

BC/BE to join 100 physician multi-specialty clinic with 4 Board Certified adult cardiologists, 3 pediatric cardiologists, 1 cardiovascular surgeon. Adjacent to 485 bed hospital with level one trauma center; dedicated heart program. Rockford Clinic is located 75 miles northwest of Chicago in a pleasant community of 250,000.

Guaranteed salary with incentive, comprehensive benefit package. Teaching opportunities. Please send CV to: Carol Kump, Director Physician Recruiting

ROCKFORD CLINIC
2300 N. Rockton Ave., Rockford, IL 61103
815 968-0051 ext. 2900

MIDWEST NONINVASIVE

Midwest metro. Group w/6 cardiologists. Excellent call, optional teaching, competitive financial package. State-of-the-art equipment, labs. Nuclear capability, TEE's, ECHOS. City w/universities, culture, sports.

Contact: Kristin Aldrich
10983 Granada
Overland Park, KS 66211
1-800-533-0525

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CAREER OPPORTUNITIES

CHICAGO AREA CARDIOLOGIST INVASIVE/NONINVASIVE POSITION AVAILABLE

for BE/BC cardiologist to join multi-specialty clinics located in north and northwest suburbs of Chicago.
Excellent starting salary and fringe benefits. Please reply with CV to:

Jose Kogan, M.D.
4801 Church St.
Skokie, IL 60077

ELECTROPHYSIOLOGIST

Join a dynamic practice in medically-sophisticated Midwest metro. A team of 5 cardiologists and 1 electrophisiologist provide comprehensive cardiology services to a drawing area of 1,000,000. 100% EP, open second EP lab. Competitive salary, benefits, and partnership potential. Academic affiliation available. Family-oriented community with good schools and cultural and collegiate aspects. Contact:

Julie Sherriff
10983 Granada, #202 • Overland Park, KS 66211
1-800-533-0525
FAX C.V. 913-451-3931

LANSING, MI

Invasive/NonInvasive cardiologist needed for July 1993 opening, for Lansing Michigan area. Attractive salary benefits package and partnership opportunity. Send resume to:

CARDIOLOGY CONSULTANTS, P.C.
5848 Executive Drive
Lansing, MI 48911

SEMINARS

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Daniel Levy, M.D.
Eric Topol, M.D.

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INFORMATION: Educational Seminars,
LAHEY CLINIC MEDICAL CENTER
41 Mall Road, Burlington, MA 01805
Telephone (617) 273-5238

#1 In Healthcare Recruitment

CHIEFS/DEPT. HEADS/DIRECTORS/FACULTY

THE UNIVERSITY OF MISSOURI-COLUMBIA

Department of Child Health/Pediatrics is seeking a pediatric cardiologist at the Associate Professor/Professor level. The position includes responsibilities in medical student and housestaff teaching, direct patient care, and research activities. Experience in invasive EPS, and preventive cardiology. Academic appointment and salary will be competitively commensurate with qualifications and experience. MD degree and Board certification is necessary. Submit application and curriculum vitae to:

Drs Zuhdi Lababidi or William Altemeier
Dept. of Child Health/Pediatrics
UNIVERSITY OF MISSOURI HEALTH SCIENCE CENTER
One Hospital Dr. • Columbia, MO 65212

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PRACTICE FOR SALE

CARDIOLOGY PRACTICE FOR SALE

Nine years old. Invasive & Noninvasive. 45 miles North of Sacramento. Contact:

Nick Capos, MD
1002 Live Oak, Yuba City, CA 95991
916-673-6140

CAREER OPPORTUNITIES

IDAHO FALLS

BC/BE Cardiologist needed to join medical staff of state-of-the-art 246-bed hospital. Beautiful community of 50,000 with total service area of 470,000 located near mountains, river-ideal place to raise family. Hospital to provide income guarantee; call is 1 in 4.

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Contact Cliff Orme (800) 285-1085
and send CV to
390 South Main, Ste. 200
Bountiful, UT 84010

A BUSY CARDIOLOGY GROUP PRACTICE

located in central New Jersey for invasive and non invasive cardiology must be board certified in internal medicine with special emphasis in nuclear cardiology.

Reply Box 1283
The American Journal of Cardiology
249 West 17th Street • NY NY 10011

NON-INVASIVE CARDIOLOGIST PHOENIX, ARIZONA

NORTH PHOENIX HEART CENTER, a progressive, well established (4) physician group in Phoenix, Arizona, is seeking a BC/BE Non-Invasive Cardiologist to complement their busy private practice. Affiliated with (4) major Valley hospitals, the center provides excellent working conditions at its (3) office locations in the Phoenix-metro area. Enjoy fantastic southwestern living year round and a competitive salary/benefit package. Please send CV to:

NORTH PHOENIX HEART CENTER
9327 N. Third Street, Suite 300
Phoenix, Arizona 85020

CARDIOLOGIST BE/BC, OREGON

The Portland Cardiovascular Institute is seeking a BE/BC invasive non-interventional cardiologist for expanding 4 physician cardiovascular group. Excellent opportunity to join established comprehensive cardiac program, including cath, PTCA, atherectomy, pacemakers, TEE, stress echo, nuclear and preventive cardiology. The Northwest offers the outdoor enthusiast unparalleled experiences. Please send your C.V. to

CARDIOLOGY ASSOCIATES
Attn: **M.L. Davis**
10000 SE Main • Suite 201 • Portland, OR 97216
or call 503-251-6310

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